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(54) Title: ANIMAL COLLAGENS AND GELATINS

(57) Abstract: The present invention provides animal collagens and gelatins and compositions thereof, and methods of producing the same.

5                          ANIMAL COLLAGENS AND GELATINS

This application is a continuation-in-part application of U.S. Application Serial No. 09/439,058,
filed 12 November 1999, the specification of which is incorporated by reference herein in its
entirety.

10
                              **FIELD OF THE INVENTION**
The present invention relates to the recombinant synthesis of collagens and gelatins derived from
animal sequences. The present invention also relates to novel polynucleotide sequences encoding
bovine and porcine collagens, and to the encoded polypeptide sequences, and to the use of such
15      sequences in the recombinant production of animal collagens and gelatins.


                           **BACKGROUND OF THE INVENTION**
The most abundant component of the extracellular matrix is collagen. Collagens are a large
family of fibrous proteins, characterized by the presence of triple-stranded helical domains.
20      Collagen molecules are generally the result of the trimeric assembly of polypeptide chains
containing $(-Gly-X-Y-)_n$ repeats which allow for the formation of triple helical domains (van der
Rest et al. (1991) FASEB J. 5:2814-2823).


**Collagen**
25      Presently, about twenty distinct collagen types have been identified in vertebrates, including
bovine, ovine, porcine, chicken, and human collagens. Generally, the collagen types are
numbered by Roman numerals, and the chains found in each collagen type are identified by
Arabic numerals. Detailed descriptions of structure and biological functions of the various
different types of naturally occurring collagens are generally available in the art. (See, e.g., Ayad
30      et al. (1998) The Extracellular Matrix Facts Book, Academic Press, San Diego, CA; Burgeson, R.
E., and Nimmi (1992) "Collagen types: Molecular Structure and Tissue Distribution" in Clin.
Orthop. 282:250-272; Kielty, C. M. et al. (1993) "The Collagen Family: Structure, Assembly
And Organization In The Extracellular Matrix," Connective Tissue And Its Heritable Disorders,
Molecular Genetics, And Medical Aspects, Royce, P. M. and B. Steinmann eds., Wiley-Liss, NY,
35      pp. 103-147; and Prockop, D.J. and K.I. Kivirikko (1995) "Collagens: Molecular Biology,
Diseases, and Potentials for Therapy," Annu. Rev. Biochem., 64:403-434.)


Type I collagen is the major fibrillar collagen of bone and skin, comprising approximately 80-
90% of an organism's total collagen. Type I collagen is the major structural macromolecule

5    present in the extracellular matrix f multicellular organisms and comprises approximately 20%
     of total protein mass. Type I collagen is a heterotrimeric molecule comprising two α1(I) chains
     and one α2(I) chain, encoded by the COL1A1 and COL1A2 genes, respectively. Other collagen
     types are less abundant than type I collagen, and exhibit different distribution patterns. For
     example, type II collagen is the predominant collagen in cartilage and vitreous humor, while type
10   III collagen is found at high levels in blood vessels and to a lesser extent in skin.

     Type II collagen is a homotrimeric collagen comprising three identical α1(II) chains encoded by
     the COL2A1 gene. Purified type II collagen may be prepared from tissues by, methods known in
     the art, for example, by procedures described in Miller and Rhodes (1982) Methods In
15   Enzymology 82:33-64.

     Type III collagen is a major fibrillar collagen found in skin and vascular tissues. Type III
     collagen is a homotrimeric collagen comprising three identical α1(III) chains encoded by the
     COL3A1 gene. Methods for purifying type III collagen from tissues can be found in, for
20   example, Byers et al. (1974) Biochemistry 13:5243-5248; and Miller and Rhodes, *supra*.

     Type IV collagen is found in basement membranes in the form of sheets rather than fibrils. Most
     commonly, type IV collagen contains two α1(IV) chains and one α2(IV) chain. The particular
     chains comprising type IV collagen are tissue-specific. Type IV collagen may be purified using,
25   for example, the procedures described in Furuto and Miller (1987) Methods in Enzymology,
     144:41-61, Academic Press.

     Type V collagen is a fibrillar collagen found in, primarily, bones, tendon, cornea, skin, and blood
     vessels. Type V collagen exists in both homotrimeric and heterotrimeric forms. One form of
30   type V collagen is a heterotrimer of two α1(V) chains and one α2(V) chain. Another form of type
     V collagen is a heterotrimer of α1(V), α2(V), and α3(V) chains. A further form of type V
     collagen is a homotrimer of α1(V). Methods for isolating type V collagen from natural sources
     can be found, for example, in Elstow and Weiss (1983) Collagen Rel. Res. 3:181-193, and Abedin
     et al. (1982) Biosci. Rep. 2:493-502.

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     Type VI collagen has a small triple helical region and two large non-collagenous remainder
     portions. Type VI collagen is a heterotrimer comprising α1(VI), α2(VI), and α3(VI) chains.
     Type VI collagen is found in many connective tissues. Descriptions of how to purify type VI

5      collagen from natural sources can be found, for example, in Wu et al. (1987) Biochem. J.
       248:373-381, and Kielty et al. (1991) J. Cell Sci. 99:797-807.

       Type VII collagen is a fibrillar collagen found in particular epithelial tissues. Type VII collagen
       is a homotrimeric molecule of three α1(VII) chains. Descriptions of how to purify type VII
10     collagen from tissue can be found in, for example, Lunstrum et al. (1986) J. Biol. Chem.
       261:9042-9048, and Bentz et al. (1983) Proc. Natl. Acad. Sci. USA 80:3168-3172.

       Type VIII collagen can be found in Descemet's membrane in the cornea. Type VIII collagen is a
       heterotrimer comprising two α1(VIII) chains and one α2(VIII) chain, although other chain
15     compositions have been reported. Methods for the purification of type VIII collagen from nature
       can be found, for example, in Benya and Padilla (1986) J. Biol. Chem. 261:4160-4169, and
       Kapoor et al. (1986) Biochemistry 25:3930-3937.

       Type IX collagen is a fibril-associated collagen found in cartilage and vitreous humor. Type IX
20     collagen is a heterotrimeric molecule comprising α1(IX), α2(IX), and α3 (IX) chains. Type IX
       collagen has been classified as a FACIT (Fibril Associated Collagens with Interrupted Triple
       Helices) collagen, possessing several triple helical domains separated by non-triple helical
       domains. Procedures for purifying type IX collagen can be found, for example, in Duance, et al.
       (1984) Biochem. J. 221:885-889; Ayad et al. (1989) Biochem. J. 262:753-761; and Grant et al.
25     (1988) The Control of Tissue Damage, Glauert, A. M., ed., Elsevier Science Publishers,
       Amsterdam, pp. 3-28.

       Type X collagen is a homotrimeric compound of α1(X) chains. Type X collagen has been
       isolated from, for example, hypertrophic cartilage found in growth plates. (See, e.g., Apte et al.
30     (1992) Eur J Biochem 206 (1):217-24.)

       Type XI collagen can be found in cartilaginous tissues associated with type II and type IX
       collagens, and in other locations in the body. Type XI collagen is a heterotrimeric molecule
       comprising α1(XI), α2(XI), and α3(XI) chains. Methods for purifying type XI collagen can be
35     found, for example, in Grant et al., *supra*.

       Type XII collagen is a FACIT collagen found primarily in association with type I collagen. Type
       XII collagen is a homotrimeric molecule comprising three α1(XII) chains. Methods for purifying

5   type XII collagen and variants thereof can be found, for example, in Dublet et al. (1989) J. Biol.
    Chem. 264:13150-13156; Lunstrum et al. (1992) J. Biol. Chem. 267:20087-20092; and Watt et al.
    (1992) J. Biol. Chem. 267:20093-20099.

    Type XIII is a non-fibrillar collagen found, for example, in skin, intestine, bone, cartilage, and
10  striated muscle. A detailed description of type XIII collagen may be found, for example, in
    Juvonen et al. (1992) J. Biol. Chem. 267:24700-24707.

    Type XIV is a FACIT collagen characterized as a homotrimeric molecule comprising $\alpha 1(XIV)$
    chains. Methods for isolating type XIV collagen can be found, for example, in Aubert-Foucher et
15  al. (1992) J. Biol. Chem. 267:15759-15764, and Watt et al., *supra*.

    Type XV collagen is homologous in structure to type XVIII collagen. Information about the
    structure and isolation of natural type XV collagen can be found, for example, in Myers et al.
    (1992) Proc. Natl. Acad. Sci. USA 89:10144-10148; Huebner et al. (1992) Genomics 14:220-224;
20  Kivirikko et al. (1994) J. Biol. Chem. 269:4773-4779; and Muragaki, J. (1994) Biol. Chem.
    264:4042-4046.

    Type XVI collagen is a fibril-associated collagen, found, for example, in skin, lung fibroblast, and
    keratinocytes. Information on the structure of type XVI collagen and the gene encoding type XVI
25  collagen can be found, for example, in Pan et al. (1992) Proc. Natl. Acad. Sci. USA 89:6565-
    6569; and Yamaguchi et al. (1992) J. Biochem. 112:856-863.

    Type XVII collagen is a hemidesmosal transmembrane collagen, also known at the bullous
    pemphigoid antigen. Information on the structure of type XVII collagen and the gene encoding
30  type XVII collagen can be found, for example, in Li et al. (1993) J. Biol. Chem. 268(12):8825-
    8834; and McGrath et al. (1995) Nat. Genet. 11(1):83-86.

    Type XVIII collagen is similar in structure to type XV collagen and can be isolated from the liver.
    Descriptions of the structures and isolation of type XVIII collagen from natural sources can be
35  found, for example, in Rehn and Pihlajaniemi (1994) Proc. Natl. Acad. Sci USA 91:4234-4238;
    Oh et al. (1994) Proc. Natl. Acad. Sci USA 91:4229-4233; Rehn et al. (1994) J. Biol. Chem.
    269:13924-13935; and Oh et al. (1994) Genomics 19:494-499.

5    Type XIX collagen is believed to be another member of the FACIT collagen family, and has been
     found in mRNA isolated from rhabdomyosarcoma cells. Descriptions of the structures and
     isolation of type XIX collagen can be found, for example, in Inoguchi et al. (1995) J. Biochem.
     117:137-146; Yoshioka et al. (1992) Genomics 13:884-886; and Myers et al., J. Biol. Chem.
     289:18549-18557 (1994).

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     Type XX collagen is a newly found member of the FACIT collagenous family, and has been
     identified in chick cornea. (See, e.g., Gordon et al. (1999) FASEB Journal 13:A1119; and
     Gordon et al. (1998), IOVS 39:S1128.)

15   **Gelatin**
     Gelatin is a derivative of collagen, a principal structural and connective protein in animals.
     Gelatin is derived from denaturation of collagen and contains polypeptide sequences having Gly-
     X-Y repeats, where X and Y are most often proline and hydroxyproline residues. These
     sequences contribute to triple helical structure and affect the gelling ability of gelatin
20   polypeptides. Currently available gelatin is extracted through processing of animal hides and
     bones, typically from bovine and porcine sources. The biophysical properties of gelatin make it a
     versatile material, widely used in a variety of applications and industries. Gelatin is used, for
     example, in numerous pharmaceutical and medical, photographic, industrial, cosmetic, and food
     and beverage products and processes of manufacture. Gelatin is thus a commercially valuable and
25   versatile product.

     Gelatin is typically manufactured from naturally occurring collagen in bovine and porcine
     sources, in particular, from hides and bones. In some instances, gelatin can be extracted from, for
     example, piscine, chicken, or equine sources. Raw materials of typical gelatin production, such as
30   bovine hides and bones, originate from animals subject to government-certified inspection and
     passed as fit for human consumption. There is concern over the infectivity of this raw material,
     due to the presence of contaminating agents such as transmissible spongiform encephalopathies
     (TSEs), particularly bovine spongiform encephalopathy (BSE), and scrapie, etc. (See, e.g.,
     Rohwer, R.G. (1996), *Dev Biol Stand* 88:247-256.) Such issues are especially critical to gelatin
35   used in pharmaceutical and medical applications.

     Recently, concern about the safety of these materials, a significant portion of which are derived
     from bovine sources, has increased, causing various gelatin-containing products to become the
     focus of several regulatory measures to reduce the potential risk of transmission of bovine

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5    spongiform encephalopathy (BSE), linked to new variant Creutzfeldt-Jakob disease (nvCJD), a
     fatal neurological disease in humans. There is concern that purification steps currently used in the
     process of extracting gelatin from animal tissues and bones may not be sufficient to remove the
     likelihood of infectivity due to contaminating SE-carrying tissue (i.e., brain tissue, etc.). U.S. and
     European manufacturers specify that raw material for gelatin to be included in animal or human
10   food products or in pharmaceutical, medical, or cosmetic applications must not be obtained from a
     growing number of BSE countries. In addition, regulations specify that certain materials, e.g.,
     bovine brain tissues, are not used in the production of gelatin.

     Current production processes involve several purification and cleansing steps, and can require
15   harsh and lengthy modes of extraction. The animal hides and bones are treated in a rendering
     process, and the extracted material is subjected to various chemical treatments, including
     prolonged exposure to highly acidic or alkaline solutions. Numerous purification steps can
     involve washing and filtration and various heat treatments. Acid demineralization and lime
     treatments are used to remove impurities such as non-collagenous proteins. Bones must be
20   degreased. Additional washing and filtration steps, ion exchanges, and other chemical and
     sterilizing treatments are added to the process to further purify the material. Furthermore,
     contaminants and impurities can still remain after processing, and the resultant gelatin product
     must thus typically be clarified, purified, and often further concentrated before being ready for
     use.
25
     Commercial gelatin is generally classified as type A or type B. These classifications reflect the
     pre-treatment extraction sources receive as part of the extraction process. Type A is generally
     derived from acid-processed materials, usually porcine hides, and type B is generally derived
     from alkaline- or lime-processed materials, usually bovine bones (ossein) and hides. In both type
30   A and B extraction processes, the resultant gelatin product typically comprises a mixture of
     gelatin molecules, in sizes of from a few thousand up to several hundred thousand Daltons.

     Fish gelatin, classified as gelling or non-gelling types, and typically processed as Type A gelatin,
     is also used in certain commercial applications. Gelling types are usually derived from the skins
35   of warm water fish, while non-gelling types are typically derived from cold water fish. Fish
     gelatins have widely varying amino acid compositions, and differ from animal gelatins in having
     typically lower proportions of proline and hydroxyproline residues. In contrast to other animal
     gelatins, fish gelatins typically remain liquid at much lower temperatures, even at comparable
     average molecular weights. As with animal gelatin, fish gelatin is extracted by treatment and

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5      subsequent hydrolyzation of fish skin. Again, as with animal extraction processes, the process of
       extracting fish gelatin results in a product that lacks homogeneity.

       Current methods of extraction thus result in a gelatin product that is a heterogeneous mixture of
       proteins, containing polypeptides with molecular weight distributions of varying ranges. It is

10     sometimes necessary to blend various lots of product in order to obtain a gelatin mixture with the
       physical properties appropriate for use in a desired application. There is thus a need for a reliable
       and reproducible means of gelatin production that provides a homogenous product with controlled
       characteristics.

15     In addition, in the pharmaceutical, cosmetic, and food and beverage industries, especially, there is
       a need for a source of gelatin other than that obtained through extraction from animal sources,
       e.g., bovine, porcine bones and tissues. Further, as currently available gelatin is manufactured
       from animal sources such as bones and tissues, there are concerns relating to the undesirable
       immunogenicity and infectivity of gelatin-containing products. (See, e.g., Sakaguchi, M. *et al.*

20     (1999) *J. Aller. Clin. Immunol.* 104:695-699; Miyazawa *et al.* (1999) *Vaccine* 17:2176-2180;
       Sakaguchi *et al.* (1999) *Immunology* 96:286-290; Kelso (1999) *J Aller. Clin Immunol.* 103:200-
       202; Asher (1999) *Dev Biol Stand* 99:41-44; and Verdrager (1999) *Lancet* 354:1304-1305.) In
       addition, the availability of a substitute material that does not undergo extraction from animal
       sources, e.g., tissues and bones, will address various ethical, religious, and social dictates. A

25     recombinant material that does not require extraction from animal sources, such as tissues and
       bones, could be used, for example, in the manufacture of foods and other ingested products,
       including encapsulated medicines, that are appropriate for use by people with dietary restrictions,
       for example, those who follow Kosher and Halal law.

30     **Post-translational Enzymes**
       Post-translational enzymes are important to the biosynthesis of collagens and collagenous
       proteins. For example, prolyl 4-hydroxylase is required to hydroxylate prolyl residues in the Y-
       position of the repeating -Gly-X-Y- sequences to 4-hydroxyproline. (See, e.g., Prockop et al.
       (1984) N. Engl. J. Med. 311:376-386.) Hydroxyproline plays a critical role for stabilization of the

35     collagen triple helix.

       Vertebrate prolyl 4-hydroxylase is an $\alpha_2\beta_2$ tetramer. (See, e.g. Berg and Prockop. (1973) J. Biol.
       Chem. 248:1175-1192; and Tuderman et al. (1975) Eur. J. Biochem. 52:9-16.) The $\alpha$ subunits
       (63 kDa) contain the catalytic sites involved in the hydroxylation of prolyl residues, and are

                                                       7

5    insoluble in the absence of β subunits. The β subunits (55 kDa), identical t protein disulfide
isomerase, catalyze thiol/disulfide interchange protein substrate, leading to the formation of a set
of disulfide bonds essential to establishing a stable protein. The β subunits retain 50% of protein
disulfide isomerase activity when part of the prolyl 4-hydroxylase tetramer. (See, e.g.,
Pihlajaniemi et al. (1987) Embo J. 6:643-649; Parkkonen et al. (1988) Biochem. J. 256:1005-
10   1011; and Koivu et al. (1987) J. Biol. Chem. 262:6447-6449.) Active recombinant human prolyl
4-hydroxylase has been produced in insect cells by simultaneously expressing the α and β
subunits. (See, e.g., Vuori et al. (1992) Proc. Natl. Acad. Sci. USA 89:7467-7470.)

In addition to prolyl 4-hydroxylase, other collagen post-translational enzymes have been
15   identified and reported in the literature, including, for example, C-proteinase, N-proteinase, lysyl
oxidase, and lysyl hydroxylase. (See, e.g., Olsen et al. (1991) Cell Biology of Extracellular
Matrix, 2nd ed., Hay editor, Plenum Press, New York.)

Expression of many exogenous genes is readily obtained in a variety of recombinant host-vector
20   systems. However, expression becomes difficult if the final formation of the protein requires
extensive post-translational processing. For example, prolyl 4-hydroxylase activity is clearly an
essential requirement for hydroxylation in nature of collagenous domains. Supplementation of
prolyl 4-hydroxylase activity is required in expression systems deficient of prolyl 4-hydroxylase
endogenous activity, in order to provide hydroxylation systems as found in nature.
25

Failure to obtain reliable and stable recombinant expression of genes for collagens has prevented
the production of collagens and gelatins that have a number of useful applications. In addition,
many types of collagen are only available in trace quantities present in tissues, and cannot be
obtained in significant quantities from these sources. Furthermore, non-collagenous impurities
30   can be left over after or introduced during the extraction and purification processes. :

Summary
In summary, although the characteristics of commercially available animal collagens and gelatins
are suitable for many products, the variability in these currently available materials, and the
35   difficulties associated with optimizing these materials for use in various applications, provide
little flexibility. As a result, there is a need in the art for an efficient system that allows the
starting material to be modified at the genetic and molecular levels, providing the potential for
producing recombinant collagens and gelatins, specifically tailored and standardized for different
applications and markets. Furthermore, existing concern over the risks of immunogenicity and

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5    infectivity associated with the use of the extracted materials currently available has established a
need for a pure and safe substitute material.

## SUMMARY OF THE INVENTION

10   The present invention provides animal collagens and gelatins, and methods of producing these
animal collagens and gelatins. Therefore, in one aspect, the present invention encompasses an
isolated and purified polypeptide comprising a bovine or porcine polypeptide selected from the
group consisting of $\alpha 1(I)$ collagens, $\alpha 2(I)$ collagens, and $\alpha 1(III)$ collagens, and fragments and
variants of these collagens.

15

In one embodiment, the invention provides an isolated and purified polypeptide comprising a
bovine $\alpha 1(I)$ collagen or fragments or variants thereof. In certain embodiments, the polypeptide
is single-chain, or homotrimeric, or heterotrimeric. In one aspect, the polypeptide comprises the
amino acid sequence of SEQ ID NO:2 or fragments or variants thereof. A composition

20   comprising the polypeptide is also provided.

In a further embodiment, the present invention encompasses an isolated and purified
polynucleotide encoding a bovine $\alpha 1(I)$ collagen or fragments or variants thereof, and an isolated
and purified polynucleotide that is complementary to the polynucleotide encoding a bovine $\alpha 1(I)$

25   collagen or fragments or variants thereof. The present invention provides, in one embodiment, an
isolated and purified polynucleotide encoding SEQ ID NO:2 or fragments or variants thereof.
Compositions, expression vectors, and host cells comprising the polynucleotide are also provided.
In various embodiments, the host cell is a prokaryotic cell or a eukaryotic cell, specifically, an
animal, yeast, plant, insect, or fungal cell. In some embodiments, the present invention provides

30   transgenic animals and transgenic plants comprising the polynucleotide. In one aspect, the
present invention encompasses a method for producing a bovine $\alpha 1(I)$ collagen, the method
comprising culturing the host cell comprising the polynucleotide under conditions suitable for
expression of the bovine $\alpha 1(I)$ collagen, and recovering the bovine $\alpha 1(I)$ collagen from the host
cell culture.

35

In certain embodiments, the present invention provides recombinant collagens and recombinant
gelatins comprising bovine $\alpha 1(I)$ collagen or fragments or variants thereof. The invention

5      specifically provides recombinant collagens and gelatins comprising SEQ ID NO:2 or fragments
       or variants thereof.

       In one embodiment, the invention provides an isolated and purified polypeptide comprising a
       bovine α1(III) collagen or fragments or variants thereof. In certain embodiments, the polypeptide
10     is single-chain, or homotrimeric, or heterotrimeric. In one aspect, the polypeptide comprises the
       amino acid sequence of SEQ ID NO:4 or SEQ ID NO:6 or fragments or variants thereof. A
       composition comprising the polypeptide is also provided.

       In a further embodiment, the present invention encompasses an isolated and purified
15     polynucleotide encoding a bovine α1(III) collagen or fragments or variants thereof, and an
       isolated and purified polynucleotide that is complementary to the polynucleotide encoding a
       bovine α1(III) collagen or fragments or variants thereof. The present invention provides, in one
       embodiment, an isolated and purified polynucleotide encoding SEQ ID NO:4 or SEQ ID NO:6 or
       fragments or variants thereof. Compositions, expression vectors, and host cells comprising the
20     polynucleotide are also provided. In various embodiments, the host cell is a prokaryotic cell or a
       eukaryotic cell, specifically, an animal, yeast, plant, insect, or fungal cell. In some embodiments,
       the present invention provides transgenic animals and transgenic plants comprising the
       polynucleotide. In one aspect, the present invention encompasses a method for producing a
       bovine α1(III) collagen, the method comprising culturing the host cell comprising the
25     polynucleotide under conditions suitable for expression of the bovine α1(III) collagen, and
       recovering the bovine α1(III) collagen from the host cell culture.

       In certain embodiments, the present invention provides recombinant collagens and recombinant
       gelatins comprising bovine α1(III) collagen or fragments or variants thereof. The invention
30     specifically provides recombinant collagens and gelatins comprising SEQ ID NO:4 or SEQ ID
       NO:6 or fragments or variants thereof.

       In one embodiment, the invention provides an isolated and purified polypeptide comprising a
       porcine α1(I) collagen or fragments or variants thereof. In certain embodiments, the polypeptide
35     is single-chain, or homotrimeric, or heterotrimeric. In one aspect, the polypeptide comprises the
       amino acid sequence of SEQ ID NO:8 or fragments or variants thereof. A composition
       comprising the polypeptide is also provided.

5    In a further embodiment, the present invention encompasses an isolated and purified
polynucleotide encoding a porcine α1(I) collagen or fragments or variants thereof, and an isolated
and purified polynucleotide that is complementary to the polynucleotide encoding a porcine α1(I)
collagen or fragments or variants thereof. The present invention provides, in one embodiment, an
isolated and purified polynucleotide encoding SEQ ID NO:8 or fragments or variants thereof.

10   Compositions, expression vectors, and host cells comprising the polynucleotide are also provided.
In various embodiments, the host cell is a prokaryotic cell or a eukaryotic cell, specifically, an
animal, yeast, plant, insect, or fungal cell. In some embodiments, the present invention provides
transgenic animals and transgenic plants comprising the polynucleotide. In one aspect, the
present invention encompasses a method for producing a porcine α1(I) collagen, the method

15   comprising culturing the host cell comprising the polynucleotide under conditions suitable for
expression of the porcine α1(I) collagen, and recovering the porcine α1(I) collageen from the host
cell culture.

In certain embodiments, the present invention provides recombinant collagens and recombinant

20   gelatins comprising porcine α1(I) collagen or fragments or variants thereof. The invention
specifically provides for recombinant collagens and gelatins comprising SEQ ID NO:8 or
fragments or variants thereof.

In one embodiment, the invention provides an isolated and purified polypeptide comprising a

25   porcine α2(I) collagen or fragments or variants thereof. In certain embodiments, the polypeptide
is single-chain, or homotrimeric, or heterotrimeric. In one aspect, the polypeptide comprises the
amino acid sequence of SEQ ID NO:10 or fragments or variants thereof. A composition
comprising the polypeptide is also provided.

30   In a further embodiment, the present invention encompasses an isolated and purified
polynucleotide encoding a porcine α2(I) collagen or fragments or variants thereof, and an isolated
and purified polynucleotide that is complementary to the polynucleotide encoding a porcine α2(I)
collagen or fragments or variants thereof. The present invention provides, in one embodiment, an
isolated and purified polynucleotide encoding SEQ ID NO:10 or fragments or variants thereof.

35   Compositions, expression vectors, and host cells comprising the polynucleotide are also provided.
In various embodiments, the host cell is a prokaryotic cell or a eukaryotic cell, specifically, an
animal, yeast, plant, insect, or fungal cell. In some embodiments, the present invention provides
transgenic animals and transgenic plants comprising the polynucleotide. In one aspect, the

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5    present invention encompasses a method for producing a porcine α2(I) collagen, the method comprising culturing the host cell comprising the polynucleotide under conditions suitable for expression of the porcine α2(I) collagen, and recovering the porcine α2(I) collagen from the host cell culture.

10   In certain embodiments, the present invention provides recombinant collagens and recombinant gelatins comprising porcine α2(I) collagen or fragments or variants thereof. The invention specifically provides for recombinant collagens and gelatins comprising SEQ ID NO:10 fragments or variants thereof.

15   In one embodiment, the invention provides an isolated and purified polypeptide comprising a porcine α1(III) collagen or fragments or variants thereof. In certain embodiments, the polypeptide is single-chain, or homotrimeric, or heterotrimeric. In one aspect, the polypeptide comprises the amino acid sequence of SEQ ID NO:12 or fragments or variants thereof. A composition comprising the polypeptide is also provided.

20   In a further embodiment, the present invention encompasses an isolated and purified polynucleotide encoding a porcine α1(III) collagen or fragments or variants thereof, and an isolated and purified polynucleotide that is complementary to the polynucleotide a porcine α1(III) collagen or fragments or variants thereof. The present invention provides, in one embodiment, an

25   isolated and purified polynucleotide encoding SEQ ID NO:12 or fragments or variants thereof.

Compositions, expression vectors, and host cells comprising the polynucleotide are also provided. In various embodiments, the host cell is a prokaryotic cell or a eukaryotic cell, specifically, an animal, yeast, plant, insect, or fungal cell. In some embodiments, the present invention provides

30   transgenic animals and transgenic plants comprising the polynucleotide. In one aspect, the present invention encompasses a method for producing a porcine α1(III) collagen, the method comprising culturing the host cell comprising the polynucleotide under conditions suitable for expression of the porcine α1(III) collagen, and recovering the porcine α1(III) collagen from the host cell culture.

35

In certain embodiments, the present invention provides recombinant collagens and recombinant gelatins comprising porcine α1(III) collagen or fragments or variants thereof. The invention

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5   specifically provides for recombinant collagens and gelatins comprising SEQ ID NO:12 or
fragments or variants thereof.

Methods for producing recombinant animal collagens and gelatins are also provided. In one
embodiment, the present invention provides a method for producing recombinant animal collagen,
10  the method comprising introducing into a host cell at least one expression vector comprising a
polynucleotide sequence encoding an animal collagen or procollagen, and at least one expression
vector comprising a polynucleotide sequence encoding a post-translational enzyme, under
conditions which permit the expression of the polynucleotides; and isolating the animal collagen.
In a further aspect, the post-translational enzyme is selected from the group consisting of prolyl
15  hydroxylase, peptidyl prolyl isomerase, collagen galactosyl hydroxylysyl glucosyl transferase,
hydroxylysyl galactosyl transferase, C-proteinase, N-proteinase, lysyl hydroxylase, and lysyl
oxidase. In one embodiment, the post-translational enzyme is selected from the same species as
the animal collagen. In another embodiment, the host cell is selected from the same species as the
animal collagen. In further embodiments, the host cell does not endogenously produce collagen,
20  or does not endogenously produce a post-translational enzyme. A host cell comprising at least
one expression vector encoding an animal and at least one expression vector encoding a post-
translational enzyme is specifically provided.

In one aspect, the present invention provides a recombinant animal collagen of one type substantially
25  free from collagen of any other type. Embodiments wherein the collagen of one type is specifically
selected from the group consisting of type I, type II, type III, type IV, type V, type VI, type VII, type
VIII, type IX, type X, type XI, type XII, type XIII, type XIV, type XV, type XVI, type XVII, type
XVIII, type XIX, and type XX collagen are specifically contemplated.

30  Methods for producing recombinant animal gelatins are also provided. In one aspect, the method
comprises providing recombinant animal collagen, and deriving recombinant animal gelatin
therefrom. In another aspect, the method comprises producing recombinant animal gelatin
directly from an altered animal collagen construct.

35                              **BRIEF DESCRIPTION OF THE FIGURES**
Figures 1A, 1B, and 1C show a nucleic acid sequence (SEQ NO:1) encoding a bovine α1(I)
collagen.

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5    Figures 2A, 2B, 2C, and 2D show the amino acid sequence (SEQ ID NO:2) of a bovine α1(I)
     collagen.

     Figures 3A, 3B, and 3C show a nucleic acid sequence (SEQ ID NO:3) encoding a bovine α1(III)
     collagen.

10
     Figures 4A, 4B, 4C, and 4D show the amino acid sequence (SEQ ID NO:4) of a bovine α1(III)
     collagen.

     Figures 5A, 5B, and 5C show a nucleic acid sequence (SEQ ID NO:5) encoding a bovine α1(III)

15   collagen.

     Figures 6A, 6B, 6C, and 6D show the amino acid sequence (SEQ ID NO:6) of a bovine α1(III)
     collagen.

20   Figures 7A, 7B, and 7C show a nucleic acid sequence (SEQ ID NO:7) encoding a porcine α1(I)
     collagen.

     Figures 8A, 8B, 8C, and 8D show the amino acid sequence (SEQ ID NO:8) encoding a porcine α1(I)
     collagen.

25
     Figures 9A, 9B, and 9C show a nucleic acid sequence (SEQ ID NO:9) encoding a porcine α2(I)
     collagen.

     Figures 10A, 10B, and 10C show the amino acid sequence (SEQ ID NO:10) of a porcine α2(I)

30   collagen.

     Figures 11A, 11B, and 11C show a nucleic acid sequence (SEQ ID NO:11) encoding a porcine
     α1(III) collagen.

35   Figures 12A, 12B, and 12C show the amino acid sequence (SEQ ID NO:12) of a porcine α1(III)
     collagen.

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5       Figures 13A, 13B, 13C, 13D, 13E, 13F, 13G, 13H, and 13I depict the translated bovine α1(I)
        collagen open reading frame sequences aligned with known human (HU), mouse (MUS), dog
        (CANIS), bullfrog (RANA), and Japanese newt (CYNPS) collagen sequences.

## DETAILED DESCRIPTION OF THE INVENTION

10
        Before the present proteins, nucleotide sequences, and methods are described, it is understood that
        this invention is not limited to the particular methodology, protocols, cell lines, vectors, and
        reagents described, as these may vary. It is also to be understood that the terminology used herein
        is for the purpose of describing particular embodiments only, and is not intended to limit the
15      scope of the present invention.

        It must be noted that as used herein, and in the appended claims, the singular forms "a," "an," and
        "the" include plural reference unless the context clearly dictates otherwise. Thus, for example,
        reference to "a host cell" is reference to one or more of such host cells and equivalents thereof
20      known to those skilled in the art, and reference to "an antibody" is a reference to one or more
        antibodies and equivalents thereof known to those skilled in the art, and so forth.

        Unless defined otherwise, all technical and scientific terms used herein have the meanings as
        commonly understood by one of ordinary skill in the art to which the invention belongs.
25      Although any methods and materials similar or equivalent to those described herein can be used
        in the practice or testing of the present invention, the preferred methods, devices, and materials
        are now described. All publications mentioned herein are incorporated herein by reference for the
        purpose of describing and disclosing the cell lines, vectors, and methodologies, etc., which are
        reported in the publications which might be used in connection with the invention. Nothing herein
30      is to be construed as an admission that the invention is not entitled to antedate such disclosure by
        virtue of prior invention. Each reference cited herein is incorporated herein by reference in its
        entirety.

        The practice of the present invention will employ, unless otherwise indicated, conventional
35      methods of chemistry, biochemistry, molecular biology, immunology and pharmacology, within
        the skill of the art. Such techniques are explained fully in the literature. See, e.g., Gennaro, A.R.,
        ed. (1990) Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co.; Colowick, S. et
        al., eds., Methods In Enzymology, Academic Press, Inc.; Handbook of Experimental
        Immunology, Vols. I-IV (D.M. Weir and C.C. Blackwell, eds., 1986, Blackwell Scientific

5      Publications); Maniatis, T. et al., eds. (1989) Molecular Cloning: A Laboratory Manual, 2$^{nd}$
       edition, Vols. I-III, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al., eds. (1999) Short
       Protocols in Molecular Biology, 4$^{th}$ edition, John Wiley & Sons; Ream et al., eds. (1998)
       Molecular Biology Techniques: An Intensive Laboratory Course, Academic Press); PCR
       (Introduction to Biotechniques Series), 2nd ed. (Newton & Graham eds., 1997, Springer Verlag).

10

**DEFINITIONS**

The term "collagen" refers to any one of the known collagen types, including collagen types I
through XX, as well as to any other collagens, whether natural, synthetic, semi-synthetic, or
recombinant. The term also encompasses procollagens. The term collagen encompasses any single-

15     chain polypeptide encoded by a single polynucleotide, as well as homotrimeric and heterotrimeric
       assemblies of collagen chains. The term "collagen" specifically encompasses variants and fragments
       thereof, and functional equivalents and derivatives thereof, which preferably retain at least one
       structural or functional characteristic of collagen, for example, a $(Gly-X-Y)_n$ domain.

20     So, for example, the term "bovine $\alpha 1(I)$ collagen" refers to a single-chain bovine $\alpha 1(I)$ collagen
       encoded by a single polynucleotide sequence, and to any corresponding procollagen, or to any
       fragment, variant, functional equivalent, or derivative thereof. The term "bovine type I collagen"
       refers to a homotrimeric or heterotrimeric collagen comprising bovine type I collagen chains, and
       to any corresponding procollagen, or to any fragment, variant, functional equivalent, or derivative

25     thereof.

The term "procollagen" refers to a procollagen corresponding to any one of the collagen types I
through XX, as well as to a procollagen corresponding to any other collagens, whether natural,
synthetic, semi-synthetic, or recombinant, that possesses additional C-terminal and/or N-terminal

30     propeptides or telopeptides that assist in trimer assembly, solubility, purification, or any other
       function, and that then are subsequently cleaved by N-proteinase, C-proteinase, or other enzymes,
       e.g., proteolytic enzymes, associated with collagen production. The term procollagen specifically
       encompasses variants and fragments thereof, and functional equivalents and derivatives thereof,
       which preferably retain at least one structural or functional characteristic of collagen, for example, a

35     $(Gly-X-Y)_n$ domain.

The term "bovine $\alpha 1(I)$" refers to a bovine $\alpha 1(I)$ collagen or functional equivalent thereof, and to
fragments and variants thereof, and to polynucleotides encoding such polypeptides from any source
whether natural, synthetic, semi-synthetic, or recombinant.

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The term "bovine α1(III)" refers to a bovine α1(III) collagen or functional equivalent thereof, to fragments and variants thereof, and to polynucleotides encoding such polypeptides from any source whether natural, synthetic, semi-synthetic, or recombinant.

10    The term "porcine α1(I)" refers to a porcine α1(I) collagen or functional equivalent thereof, to fragments and variants thereof, and to polynucleotides encoding such polypeptides from any source whether natural, synthetic, semi-synthetic, or recombinant.

The term "porcine α2(I)" refers to a porcine α2(I) collagen or functional equivalent thereof, to
15    fragments and variants thereof, and to polynucleotides encoding such polypeptides from any source whether natural, synthetic, semi-synthetic, or recombinant.

The term "porcine α1(III)" refers to a porcine αI(III) collagen or functional equivalent thereof, to fragments and variants thereof, and to polynucleotides encoding such polypeptides from any source
20    whether natural, synthetic, semi-synthetic, or recombinant.

"Gelatin" as used herein refers to any gelatin, whether extracted by traditional methods or recombinant or biosynthetic in origin, or to any molecule having at least one structural and/or functional characteristic of gelatin. Gelatin is currently obtained by extraction from collagen
25    derived from animal (e.g., bovine, porcine, rodent, chicken, equine, piscine) sources, e.g., bones and tissues. The term gelatin encompasses both the composition of more than one polypeptide included in a gelatin product, as well as an individual polypeptide contributing to the gelatin material. Thus, the term recombinant gelatin as used in reference to the present invention encompasses both a recombinant gelatin material comprising the present gelatin polypeptides, as
30    well as an individual gelatin polypeptide of the present invention.

Polypeptides from which gelatin can be derived are polypeptides such as collagens, procollagens, and other polypeptides having at least one structural and/or functional characteristic of collagen. Such a polypeptide could include a single collagen chain, or a collagen homotrimer or heterotrimer,
35    or any fragments, derivatives, oligomers, polymers, or subunits thereof, containing at least one collagenous domain (a Gly-X-Y region). The term specifically contemplates engineered sequences not found in nature, such as altered collagen constructs, etc. An altered collagen construct is a

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polynucleotide comprising a sequence that is altered, through deletions, additions, substitutions, or other changes, from the naturally occurring collagen gene.

An "adjuvant" is any agent added to a drug or vaccine to increase, improve, or otherwise aid its effect. An adjuvant used in a vaccine formulation might be an immunological agent that improves the immune response by producing a non-specific stimulator of the immune response. Adjuvants are often used in non-living vaccines.

The terms "allele" or "allelic sequence" refer to alternative forms of genetic sequences. Alleles may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" polynucleotide sequences include those with deletions, insertions, or substitutions of different nucleotides resulting in a polynucleotide that encodes the same or a functionally equivalent polypeptide. Included within this definition are sequences displaying polymorphisms that may or may not be readily detectable using particular oligonucleotide probes or through deletion of improper or unexpected hybridization to alleles, with a locus other than the normal chromosomal locus for the subject polynucleotide sequence.

"Altered" polypeptides may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent polypeptide. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the biological or immunological activity of the encoded polypeptide is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid; positively charged amino acids may include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine, glycine and alanine, asparagine and glutamine, serine and threonine, and phenylalanine and tyrosine.

"Amino acid" or "polypeptide" sequences or "polypeptides," as these terms are used herein, refer to oligopeptide, peptide, polypeptide, or protein sequences, and fragments thereof, and to naturally

5      occurring or synthetic m lecules.  Polypeptide or amino acid fragments are any portion of a
       polypeptide which retains at least one structural and/or functional characteristic of the polypeptide.
       In at least one embodiment of the present invention, polypeptide fragments are those retaining at
       least one (Gly-X-Y)$_n$ region.

10     The term "animal" as it is used in reference, for example, to "animal collagens"encompasses any
       collagens, whether natural, synthetic, semi-synthetic, or recombinant.  Animal sources include, for
       example, mammalian sources, including, but not limited to, bovine, porcine, equine, rodent, and
       ovine sources, and other animal sources, including, but not limited to, chicken and piscine sources,
       and non-vertebrate sources.

15

       "Antigenicity" relates to the ability of a substance to, when introduced into the body, stimulate the
       immune response and the production of an antibody.  An agent displaying the property of
       antigenicity is referred to as being antigenic.  Antigenic agents can include, but are not limited to,
       a variety of macromolecules such as, for example, proteins, lipoproteins, polysaccharides, nucleic

20     acids, bacteria and bacterial components, and viruses and viral components.

       The terms "complementary" or "complementarity," as used herein, refer to the natural binding of
       polynucleotides by base-pairing.  For example, the sequence "A-G-T" binds to the complementary
       sequence "T-C-A."  Complementarity between two single-stranded molecules may be "partial,"

25     when only some of the nucleic acids bind, or may be complete, when total complementarity exists
       between the single stranded molecules.  The degree of complementarity between nucleic acid strands
       has significant effects on the efficiency and strength of hybridization between nucleic acid strands.
       This is of particular importance in amplification reactions, which depend upon binding between
       nucleic acids strands, and in the design and use, for example, of peptide nucleic acid (PNA)

30     molecules.

       A "deletion" is a change in an amino acid or nucleotide sequence that results in the absence of one
       or more amino acid residues or nucleotides.

35     The term "derivative," as applied to polynucleotides, refers to the chemical modification of a
       polynucleotide encoding a particular polypeptide or complementary to a polynucleotide encoding
       a particular polypeptide.  Such modifications include, for example, replacement of hydrogen by
       an alkyl, acyl, or amino group.  As used herein to refer to polypeptides, the term "derivative"
       refers to a polypeptide which is modified, for example, by hydroxylation, glycosylation,

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5     pegylation, or by any similar process. The term "derivatives" encompasses those molecules
containing at least one structural and/or functional characteristic of the molecule from which it is
derived.

A molecule is said to be a "chemical derivative" of another molecule when it contains additional
10    chemical moieties not normally a part of the molecule. Such moieties can improve the molecule's
solubility, absorption, biological half-life, and the like. The moieties can alternatively decrease
the toxicity of the molecule, eliminate or attenuate any undesirable side effect of the molecule,
and the like. Moieties capable of mediating such effects are generally available in the art and can
be found for example, in Remington's Pharmaceutical Sciences, *supra*. Procedures for coupling
15    such moieties to a molecule are well known in the art.

An "excipient" as the term is used herein is any inert substance used as a diluent or vehicle in the
formulation of a drug, a vaccine, or other pharmaceutical composition, in order to confer a
suitable consistency or form to the drug, vaccine, or pharmaceutical composition.

20
The term "functional equivalent" as it is used herein refers to a polypeptide or polynucleotide that
possesses at least one functional and/or structural characteristic of a particular polypeptide or
polynucleotide. A functional equivalent may contain modifications that enable the performance
of a specific function. The term "functional equivalent" is intended to include fragments,
25    mutants, hybrids, variants, analogs, or chemical derivatives of a molecule.

A "fusion protein" is a protein in which peptide sequences from different proteins are operably
linked.

30    The term "hybridization" refers to the process by which a nucleic acid sequence binds to a
complementary sequence through base pairing. Hybridization conditions can be defined by, for
example, the concentrations of salt or formamide in the prehybridization and hybridization solutions,
or by the hybridization temperature, and are well known in the art. Hybridization can occur under
conditions of various stringency.

35
In particular, stringency can be increased by reducing the concentration of salt, increasing the
concentration of formamide, or raising the hybridization temperature. For example, for purposes of
the present invention, hybridization under high stringency conditions occurs in about 50%
formamide at about 37°C to 42°C, and under reduced stringency conditions in about 35% to 25%

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5    formamide at about 30°C to 35°C. In particular, hybridization occurs in conditions of highest
     stringency at 42°C in 50% formamide, 5X SSPE, 0.3% SDS, and 200 μg/ml sheared and denatured
     salmon sperm DNA.

     The temperature range corresponding to a particular level of stringency can be further narrowed by
10   methods known in the art, for example, by calculating the purine to pyrimidine ratio of the nucleic
     acid of interest and adjusting the temperature accordingly. To remove nonspecific signals, blots can
     be sequentially washed, for example, at room temperature under increasingly stringent conditions of
     up to 0.1X SSC and 0.5% SDS. Variations on the above ranges and conditions are well known in
     the art.
15

     "Immunogenicity" relates to the ability to evoke an immune response within an organism. An
     agent displaying the property of immunogenicity is referred to as being immunogenic. Agents
     can include, but are not limited to, a variety of macromolecules such as, for example, proteins,
     lipoproteins, polysaccharides, nucleic acids, bacteria and bacterial components, and viruses and
20   viral components. Immunogenic agents often have a fairly high molecular weight (usually greater
     than 10 kDa).

     "Infectivity" refers to the ability to be infective or the ability to produce infection, referring to the
     invasion and multiplication of microorganisms, such as bacteria or viruses within the body.
25

     The terms "insertion" or "addition" refer to a change in a polypeptide or polynucleotide sequence
     resulting in the addition of one or more amino acid residues or nucleotides, respectively, as
     compared to the naturally occurring molecule.

30   The term "isolated" as used herein refers to a molecule separated not only from proteins, etc., that
     are present in the natural source of the protein, but also from other components in general, and
     preferably refers to a molecule found in the presence of, if anything, only a solvent, buffer, ion, or
     other component normally present in a solution of the same. As used herein, the terms "isolated"
     and "purified" do not encompass molecules present in their natural source.
35

     The term "microarray" refers to any arrangement of nucleic acids, amino acids, antibodies, etc., on a
     substrate. The substrate can be any suitable support, e.g., beads, glass, paper, nitrocellulose, nylon,
     or any appropriate membrane, etc. A substrate can be any rigid or semi-rigid support including, but
     not limited to, membranes, filters, wafers, chips, slides, fibers, beads, including magnetic or

5    nonmagnetic beads, gels, tubing, plates, polymers, microparticles, capillaries, etc. The substrate can
     provide a surface for coating and/or can have a variety of surface forms, such as wells, pins,
     trenches, channels, and pores, to which the nucleic acids, amino acids, etc., may be bound.

     The term "microorganism" can include, but is not limited to, viruses, bacteria, Chlamydia,
10   rickettsias, mycoplasmas, ureaplasmas, fungi, and parasites, including infectious parasites such as
     protozoans.

     The terms "nucleic acid" or "polynucleotide" sequences or "polynucleotides" refer to
     oligonucleotides, nucleotides, or polynucleotides, or any fragments thereof, and to DNA or RNA
15   of natural or synthetic origin which may be single- or double-stranded and may represent the
     sense or antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like
     material, natural or synthetic in origin. Polynucleotide fragments are any portion of a
     polynucleotide sequence that retains at least one structural or functional characteristic of the
     polynucleotide. In one embodiment of the present invention, polynucleotide fragments are those
20   that encode at least one (Gly-X-Y)$_n$ region. Polynucleotide fragments can be of variable length,
     for example, greater than 60 nucleotides in length, at least 100 nucleotides in length, at least 1000
     nucleotides in length, or at least 10,000 nucleotides in length.

     The phrase "percent similarity" (% similarity) refers to the percentage of sequence similarity
25   found in a comparison of two or more polypeptide or polynucleotide sequences. Percent
     similarity can be determined by methods well-known in the art. For example, percent similarity
     between amino acid sequences can be calculated using the Clustal method. (See, e.g., Higgins, D.
     G. and P. M. Sharp (1988) Gene 73:237-244.) The Clustal algorithm groups sequences into
     clusters by examining the distances between all pairs. The clusters are aligned pairwise and then
30   in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and
     sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues
     in sequence A, minus the number of gap residues in sequence B, into the sum of the residue
     matches between sequence A and sequence B, times one hundred. Gaps of low or of no homology
     between the two amino acid sequences are not included in determining percentage similarity.
35   Percent similarity can be calculated by other methods known in the art, for example, by varying
     hybridization conditions, and can be calculated electronically using programs such as the
     MEGALIGN program (DNASTAR Inc., Madison, Wisconsin).

5      As used herein, the term "plant" includes reference to one or more plants, i.e., any eukaryotic
       autotrophic organisms, such as angiosperms and gymnosperms, monotyledons and dicotyledons,
       etc., including, but not limited to, soybean, cotton, alfalfa, flax, tomato, sugar, beet, sunflower,
       potato, tobacco, maize, wheat, rice, lettuce, banana, cassava, safflower, oilseed, rape, mustard,
       canola, hemp, algae, kelp, etc. The term "plant" also encompasses one or more plant cells. The
10     term "plant cells" includes, but is not limited to, vegetative tissues and organs such as seeds,
       suspension cultures, embryos, meristematic regions, callus tissue, leaves, roots, shoots,
       gametophytes, sporophytes, pollen, tubers, corms, bulbs, flowers, fruits, cones, microspores, etc.

       The term "post-translational enzyme" refers to any enzyme that catalyzes post-translational
15     modification of, for example, any collagen or procollagen. The term encompasses, but is not
       limited to, for example, prolyl hydroxylase, peptidyl prolyl isomerase, collagen galactosyl
       hydroxylysyl glucosyl transferase, hydroxylysyl galactosyl transferase, C-proteinase, N-
       proteinase, lysyl hydroxylase, and lysyl oxidase.

20     As used herein, the term "promoter" generally refers to a regulatory region of nucleic acid
       sequence capable of initiating, directing, and mediating the transcription of a polynucleotide
       sequence. Promoters may additionally comprise recognition sequences, such as upstream or
       downstream promoter elements, which may influence the transcription rate.

25     The term "non-constitutive promoters" refers to promoters that induce transcription via a specific
       tissue, or may be otherwise under environmental or developmental controls, and includes
       repressible and inducible promoters such as tissue-preferred, tissue-specific, and cell type-specific
       promoters. Such promoters include, but are not limited to, the AdH1 promoter, inducible by
       hypoxia or cold stress, the Hsp70 promoter, inducible by heat stress, and the PPDK promoter,
30     inducible by light.

       Promoters which are "tissue-preferred" are promoters that preferentially initiate transcription in
       certain tissues. Promoters which are "tissue-specific" are promoters that initiate transcription only
       in certain tissues. "Cell type-specific" promoters are promoters which primarily drive expression
35     in certain cell types in at least one organ, for example, vascular cells.

       "Inducible" or "repressible" promoters are those under control of the environment, such that
       transcription is effected, for example, by an environmental condition such as anaerobic
       conditions, the presence of light, biotic stresses, etc., or in response to internal, chemical, or

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5    biological signals, e.g., glyceraldehyde phosphate dehydrogenase, AOX1 and AOX2 methanol-
     inducible promoters, or to physical damage.

     As used herein, the term "constitutive promoters" refers to promoters that initiate, direct, or
     mediate transcription, and are active under most environmental conditions and states of
10   development or cell differentiation.  Examples of constitutive promoters, include, but are not
     limited to, the cauliflower mosaic virus (CaMv) 35S, the 1'- or 2'- promoter derived from T-DNA
     of *Agrobacteriuam tumefaciens*, the ubiquitin 1 promoter, the Smas promoter, the cinnamyl
     alcohol dehydrogenase promoter, glyceraldehyde dehydrogenase promoter, and the *Nos* promoter,
     etc.

15

     The term "purified" as it is used herein denotes that the indicated molecule is present in the
     substantial absence of other biological macromolecules, e.g., polynucleotides, proteins, and the
     like.  The term preferably contemplates that the molecule of interest is present in a solution or
     composition at least 80% by weight; preferably, at least 85% by weight; more preferably, at least
20   95% by weight; and, most preferably, at least 99.8% by weight.  Water, buffers, and other small
     molecules, especially molecules having a molecular weight of less than about one kDa, can be
     present.

     The term "substantially purified", as used herein, refers to nucleic or amino acid sequences that
25   are removed from their natural environment, isolated or separated, and are at least 60% free,
     preferably 75% free, and most preferably 90% free from other components with which they are
     naturally associated.

     A "substitution" is the replacement of one or more amino acids or nucleotides by different amino
30   acids or nucleotides, respectively.

     The term "transfection" as used herein refers to the process of introducing an expression vector
     into a cell.  Various transfection techniques are known in the art, for example, microinjection,
     lipofection, or the use of a gene gun.

35

     "Transformation", as defined herein, describes a process by which exogenous nucleic acid
     sequences, e.g., DNA, enters and changes a recipient cell.  Transformation may occur under natural
     or artificial conditions using various methods well known in the art.  Transformation may rely on
     any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or

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5      eukaryotic host cell. The method is selected based on the type of host cell being transformed and
       may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and
       particle bombardment. Such "transformed" cells include stably transformed cells in which the
       inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of
       the host chromosome, and also include cells which transiently express the inserted nucleic acid for
10     limited periods of time.

       As used herein, the term "vaccine" refers to a preparation of killed or modified microorganisms,
       living attenuated organisms, or living fully virulent organisms, or any other agent, including, but
       not limited to peptides, proteins, biological macromolecules, or nucleic acids, natural, synthetic,
15     or semi-synthetic, administered to produce or artificially increase immunity to a particular
       disease, in order to prevent future infection with a similar entity. Vaccines can be live or
       inactivated microorganisms or agents, including viruses and bacteria, as well as subunit, synthetic,
       semi-synthetic, or recombinant DNA-based.

20     Vaccines can be monovalent (a single strain/microorganism/disease vaccine) consisting of one
       microorganism or agent (e.g., poliovirus vaccine) or the antigens of one microorganism or agent.
       Vaccines can also be multivalent, e.g., divalent, trivalent, etc. (a combined vaccine), consisting of
       more than one microorganism or agent (e.g., a measles-mumps-rubella (MMR) vaccine) or the
       antigens of more than one microorganism or agent.
25
       Live vaccines are prepared from living microorganisms. Attenuated vaccines are live vaccines
       prepared from microorganisms which have undergone physical alteration (such as radiation or
       temperature conditioning) or serial passage in laboratory animal hosts or infected tissue/cell
       cultures, such treatments producing avirulent strains or strains of reduced virulence, but
30     maintaining the capability of inducing protective immunity. Examples of live attenuated vaccines
       include measles, mumps, rubella, and canine distemper. Inactivated vaccines are vaccines in
       which the infectious microbial components have been destroyed, e.g., by chemical or physical
       treatment (such as formalin, beta-propiolactone, or gamma radiation), without affecting the
       antigenicity or immunogenicity of the viral coat or bacterial outer membrane proteins. Examples
35     of inactivated or subunit vaccines include influenza, Hepatitis A, and poliomyelitis (IPV)
       vaccines.

       Subunit vaccines are composed of key macromolecules from, e.g., the viral, bacterial, or other
       agent responsible for eliciting an immune response. These components can be obtained in a

                                                    25

number of ways, for example, through purification from microorganisms, generation using recombinant DNA technology, etc. Subunit vaccines can contain synthetic mimics of any infective agent. Subunit vaccines can include macromolecules such as bacterial protein toxins (e.g., tetanus, diphtheria), viral proteins (e.g., from influenza virus), polysaccharides from encapsulated bacteria (e.g., from *Haemophilus influenzae* and *Streptococcus pneumonia*), and viruslike particles produced by recombinant DNA technology (e.g., hepatitis B surface antigen), etc.

Synthetic vaccines are vaccines made up of small synthetic peptides that mimic the surface antigens of pathogens and are immunogenic, or may be vaccines manufactured with the aid of recombinant DNA techniques, including whole viruses whose nucleic acids have been modified.

Semi-synthetic vaccines, or conjugate vaccines, consist of polysaccharide antigens from microorganisms attached to protein carrier molecules.

DNA vaccines contain recombinant DNA vectors encoding antigens, which, upon expression of the encoded antigen in host cells having taken up the DNA, induce humoral and cellular immune responses against the encoded antigens.

Vaccines have been developed for a variety of infectious agents. The present invention is directed to recombinant gelatins that can be used in vaccine formulations regardless of the agent involved, and are thus not limited to use in the vaccines specifically described herein by way of example. Vaccines include, but are not limited to, vaccines for vacinnia virus (small pox), polio virus (Salk and Sabin), mumps, measles, rubella, diphtheria, tetanus, Varicella-Zoster (chicken pox/shingles), pertussis (whopping cough), Bacille Calmette-Guerin (BCG, tuberculosis), haemophilus influenzae meningitis, rabies, cholera, Japanese encephalitis virus, salmonella typhi, shigella, hepatitis A, hepatitis B, adenovirus, yellow fever, foot-and-mouth disease, herpes simplex virus, respiratory syncytial virus, rotavirus, Dengue, West Nile virus, Turkey herpes virus (Marek's Disease), influenza, and anthrax. The term vaccine as used herein includes reference to vaccines to various infectious and autoimmune diseases and cancers that have been or that will be developed, for example, vaccines to various infectious and autoimmune diseases and cancers, e.g., vaccines to HIV, HCV, malaria, and vaccines to breast, lung, colon, renal, bladder, and ovarian cancers.

5      A polypeptide or amino acid "variant" is an amino acid sequence that is altered by one or more amino acids from a particular amino acid sequence. A polypeptide variant may have conservative changes, wherein a substituted amino acid has similar structural or chemical properties to the amino acid replaced, e.g., replacement of leucine with isoleucine. A variant may also have nonconservative changes, in which the substituted amino acid has physical properties different from those of the

10     replaced amino acid, e.g., replacement of a glycine with a tryptophan. Analogous minor variations may also include amino acid deletions or insertions, or both. Preferably, amino acid variants retain certain structural or functional characteristics of a particular polypeptide. Guidance in determining which amino acid residues may be substituted, inserted, or deleted may be found, for example, using computer programs well known in the art, such as LASERGENE software (DNASTAR Inc.,

15     Madison, WI).

A polynucleotide variant is a variant of a particular polynucleotide sequence that preferably has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence similarity to the particular polynucleotide sequence. It will be

20     appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of variant polynucleotide sequences encoding a particular protein, some bearing minimal homology to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon

25     choices. These combinations are made in accordance with the standard codon triplet genetic code, and all such variations are to be considered as being specifically disclosed.

**Invention**

The present invention provides for the production of recombinant animal collagens and gelatins.

30     These animal collagens and gelatins provide advantages over currently available materials in that they are produced as well-characterized and pure proteins. Methods for producing these animal collagens and gelatins are also provided. In certain embodiments, the present invention provides animal collagens and gelatins derived from bovine type I collagen, bovine type III collagen, porcine type I collagen, and porcine type III collagen. In specific embodiments, bovine $\alpha1(I)$,

35     bovine $\alpha1(III)$, porcine $\alpha1(I)$, porcine $\alpha2(I)$, and porcine $\alpha1(III)$ collagens and gelatins are provided.

The present invention provides for production of relatively large amounts of single types of animal collagen, synthesized in recombinant cell culture systems that do not make any other

5    collagen types. For example, the present invention provides animal collagen type I that is
     substantially free from any other collagen type. Using methods of the present invention,
     purification of collagen is greatly facilitated.

     The present invention is further directed to vectors and plasmids used in the methods of the
10   invention. These vectors and/or plasmids are comprised of a polynucleotide encoding the desired
     collagen, or fragments or variants thereof, necessary promoters, and other sequences necessary for
     the proper expression of such polypeptides. The polynucleotide encoding a collagen is preferably
     obtained from animal sources. Animal sources include non-human mammalian sources, such as
     bovine, ovine, and porcine sources. In one embodiment, the vectors and plasmids of the present
15   invention further include at least one polynucleotide encoding one or more post-translational
     enzymes or functional equivalents thereof. The polynucleotide encoding one or more post-
     translational enzymes may be derived from any of the above-mentioned species. In a preferred
     embodiment, the collagen-encoding polynucleotide is derived from the same species as the
     polynucleotide encoding the post-translational enzyme.

20
     In a further embodiment, at least one polynucleotide encoding a post-translational enzyme, such as
     prolyl 4-hydroxylase, C-proteinase, N-proteinase, lysyl oxidase, or lysyl hydroxylase, is inserted into
     cells that do not naturally produce post-translational enzymes, such as yeast cells, or may not
     naturally produce sufficient amounts of post-translational enzymes, such as some mammalian and
25   insect cells. In a preferred embodiment of the present invention, the post-translational enzyme is
     prolyl 4-hydroxylase, wherein the polynucleotides encoding an α subunit of prolyl 4-hydroxylase
     and the polynucleotides encoding a β subunit of prolyl 4-hydroxylase are inserted into a cell to
     produce a biologically active prolyl 4-hydroxylase enzyme.

30   The present invention specifically contemplates the use of any compound, biological or chemical,
     that confers hydroxylation, e.g., proline hydroxylation and/or lysine hydroxylation, etc., as desired,
     to the present recombinant animal collagens and gelatins. This includes, for example, prolyl 4-
     hydroxylase from any species, endogenously or exogenously supplied, including various isoforms of
     prolyl 4-hydroxylase and any variants or fragments or subunits of prolyl 4-hydroxylase having the
35   desired activity, whether native, synthetic, or semi-synthetic, and other hydroxylases such as prolyl
     3-hydroxylase, etc. (See, e.g., U.S. Patent No. 5,928,922), incorporated by reference herein in its
     entirety.) In one embodiment, the prolyl hydroxylase activity is conferred by a prolyl hydroxylase
     derived from the same species as the polynucleotide encoding recombinant collagen or gelatin, or

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5       encoding a polypeptide from which recombinant gelatin can be derived. In a further embodiment,
        the prolyl 4-hydroxylase is from an animal and the encoding polynucleotide is derived from
        sequence from the same animal.

        The present invention provides a method for producing recombinant animal collagens and gelatins.
10      It is to be noted that while, for clarity, the present methods of production are directed generally to the
        production of collagens, the production methods can be applied to the production of gelatins directly
        from altered collagen constructs, and the production of polypeptides from which gelatins can be    .
        derived. In one embodiment, the method comprises introducing into a host cell, under conditions
        suitable for expression, an expression vector encoding an animal collagen or procollagen, or
15      fragments or variants thereof, and a second expression vector encoding a post-translational enzyme,
        and isolating the collagen. In a preferred embodiment, the post translational enzyme is prolyl
        hydroxylase. (See, e.g., U.S. Patent No. 5,593,859, incorporated by reference herein in its entirety.)

        The present invention further provides animal collagens comprising at least one animal collagen
20      chain or subunit, or fragment or variants thereof. In a preferred embodiment, the collagen
        composition of the present invention comprises a collagen chain, or fragment or variant thereof, that
        is comprised of a structural amino acid pattern of $(Gly-X-Y)_n$, wherein X and Y can be any amino
        acid. Preferably, the amino acids of X and/or Y are either proline or hydyroxyproline; glycine (Gly)
        is in every third residue position of each chain; and the number of repeating Gly-X-Y triplets is of
25      about 10-3000 (i.e., n = 10-3000). The Gly-X-Y unit within a collagen chain, or subunit or
        fragment thereof, is the same or different. In one aspect, the collagen compositions of the present
        invention are less than fully glycosolated or less than fully hydroxylated. For example, the collagen
        of the present invention may be deglycosolated, unglycosolated, partially glycosolated, and partially
        hydroxylated. In a further aspect of the present invention, the collagen compositions are comprised
30      of one type of collagen, and are substantially free from any other type of collagen. In one
        embodiment, the present invention provides, a recombinant collagen type I composition substantially
        free from any other collagen, e.g., of types II through XX, etc.

        The invention further comprises recombinant polypeptides, including fusion products produced from
35      chimeric genes wherein, for example, relevant epitopes of collagen can be manufactured for
        therapeutic and other uses. Furthermore, the present invention encompasses any modifications made
        to the collagens or gelatins or compositions thereof or any degradation products thereof. Such
        modifications include, for example, processing of animal collagens or collagenous proteins and
        gelatin.

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5      The present invention further provides gelatin compositions. Specifically, the present invention
       provides gelatin compositions derived from animal collagens. In various embodiments, the gelatin
       composition is derived from bovine, porcine, or piscine collagen. In another aspect of the present
       invention, the composition is composed of a gelatin derived from a collagen type substantially free
10     from any other collagen type. In a further aspect of the present invention, the gelatin composition is
       comprised of denatured triple helices, and includes at least one collagen subunit or chain, or
       fragment or variant thereof.

       The present invention further provides methods of producing a gelatin by expressing collagen or
15     functional equivalents thereof, and deriving gelatin therefrom. The present invention further
       provides for direct expression of recombinant animal gelatin from an altered animal collagen
       construct. (See, e.g., commonly owned, co-pending application U.S. Application Serial No. ____,
       entitled "Recombinant Gelatins," filed 10 November 00, and incorporated herein by reference in
       its entirety.) More specifically, the process involves inserting into a cell an expression vector
20     comprising at least one polynucleotide encoding an animal collagen, or fragments or variants
       thereof, and an expression vector comprising at least one polynucleotide encoding a collagen
       post-translational enzyme or subunit thereof, recovering the collagen, and deriving gelatin from
       the collagen.

25     In some embodiments of the present invention, the gelatin compositions may be obtained directly
       from the isolated collagen or from biomass or culture media. Methods, processes, and techniques of
       producing gelatin compositions from collagen include denaturing the triple helical structure of the
       collagen utilizing detergents, heat or denaturing agents. Additionally, these methods, processes, and
       techniques include, but are not limited to, treatments with strong alkali or strong acids, heat
30     extraction in aqueous solution, ion exchange chromatography, cross-flow filtration and heat drying,
       and other methods known in the art that may be applied to collagen to produce the gelatin
       compositions. The same methods, processes, and techniques may be applied to biomass or culture
       media to produce the gelatin compositions of the present invention.

35     The present invention further relates to various animal collagens. In one aspect, the present
       invention provides a bovine type I collagen and a bovine type III collagen. In specific
       embodiments, a bovine $\alpha 1$(I) collagen and a bovine $\alpha 1$(III) collagen and fragments and variants
       thereof are provided.

30

5      In another aspect, the present invention provides porcine type I and porcine type III c llagens. In
       addition, the present invention provides a porcine α1(I) collagen, a porcine α2(I) collagen, and a
       porcine α1(III) collagen, and fragments and variants thereof.

       The present invention also provides polynucleotides encoding bovine α1(I) collagen, bovine α1(III)
10     collagen, porcine α1(I) collagen, or a porcine α1(III) collagen, or porcine α2(I) collagen, or
       fragments or variants thereof. The invention further provides polynucleotides complementary to the
       encoding polynucleotides, as well as polynucleotides that hybridize, under stringent conditions, to
       these nucleic acid sequences. The present invention also provides methods of producing
       recombinant bovine type I collagens, bovine type III collagens, porcine type I collagens, or porcine
15     type III collagens or fragments or variants thereof.

       In another aspect of the present invention, the expression vectors comprising the polynucleotides of
       the present invention may be inserted into host cells to produce animal collagens or gelatins, for
       example, bovine type I, bovine type III, porcine type I, and porcine type III collagens or gelatins. In
20     one method, an expression vector comprising a polynucleotide of the present invention is co-
       expressed in host cells with an expression vector comprising a polynucleotide encoding a
       polypeptide of the present invention with an expression vector comprising a polynucleotide encoding
       a post-translational enzyme. In one embodiment, the post-translational enzyme is prolyl 4-
       hydroxylase, comprising an α subunit and a β subunit.
25
       The recombinant animal collagens and gelatins of the present invention limit human exposure to
       various contaminants that may be present in animal tissues currently used as raw material in the
       manufacture of collagens and collagen-derived materials such as gelatin. Moreover, the collagens
       and gelatins of the present invention are more reproducible than collagens or gelatins currently
30     obtained from raw animal sources.

       In accordance with the invention, encoding polynucleotide sequences, as well as being well-
       characterized proteins with predictable performance may be used to generate recombinant molecules
       that direct the expression of the present polypeptides in appropriate host cells.
35
       Nucleic acid sequences encoding collagens have been generally described in the art. (See, e.g.,
       Fuller and Boedtker (1981) Biochemistry 20:996-1006; Sandell et al. (1984) J Biol Chem. 259:7826-
       34; Kohno et al. (1984) J Biol Chem. 259:13668-13673; French et al. (1985) Gene 39:311-312;
       Metsaranta et al. (1991) J Biol Chem. 266:16862-16869; Metsaranta et al, (1991) Biochim Biophys

5    Acta 1089:241-243; Wood et al. (1987) Gene 61:225-230; Glumoff et al. (1994) Biochim Biophys
     Acta 1217:41-48; Shirai et al. (1998) Matrix Biology 17:85-88; Tromp et al. (1988) Biochem J.
     253:919-912; Kuivaniemi et al. (1988) Biochem J. 252:633-640; and Ala-Kokko et al. (1989)
     Biochem J. 260:509-516.)

10   In one embodiment, the present invention provides a polynucleotide sequence comprising an
     isolated and purified polynucleotide sequence having greater than 70% similarity to the bovine
     α1(I) collagen polynucleotide sequence present in SEQ ID NO:1, or fragments or variants thereof,
     preferably greater than 80% similarity, and more preferably greater than 90% similarity. In a
     further embodiment, the polynucleotide sequence encodes the bovine α1(I) collagen amino acid
15   sequence of SEQ ID NO:2, or fragments or variants thereof.

     In another embodiment, the polynucleotide sequence of the present invention comprises an
     isolated and purified polynucleotide sequence having greater than 70% similarity to the bovine
     α1(III) collagen polynucleotide sequence of SEQ ID NO:3 or of SEQ ID NO:5, or fragments or
20   variants thereof, preferably greater than 80% similarity, and more preferably greater than 90%
     similarity. In one embodiment, the polynucleotide sequence encodes the bovine α1(III) sequence
     of SEQ ID NO:4 or of SEQ ID NO:6, or fragments or variants thereof.

     In one aspect, the present invention provides an isolated and purified polynucleotide sequence
25   comprising a polynucleotide having greater than 70% similarity to the porcine α1(I) collagen
     polynucleotide sequence present in SEQ ID NO:7, or fragments or variants thereof, preferably
     greater than 80% similarity, and more preferably greater than 90% similarity. In one
     embodiment, the polynucleotide encodes the amino acid sequence of SEQ ID NO:8, or fragments
     or variants thereof.

30
     In another aspect, the present invention contemplates an isolated and purified polynucleotide
     sequence comprising a sequence with greater than 70% similarity to the porcine α2(I) collagen
     polynucleotide sequence present in SEQ ID NO:9, or fragments or variants thereof, preferably
     greater than 80% similarity, and more preferably greater than 90% similarity. In one
35   embodiment, the polynucleotide sequence encodes the porcine α2(I) amino acid sequence of SEQ
     ID NO:10, or fragments or variants thereof.

5    In a further aspect, the present invention relates to an isolated and purified polynucleotide
      sequence having greater than 70% similarity to the porcine α1(III) collagen polynucleotide
      sequence present in SEQ ID NO:11, or fragments or variants thereof, preferably greater than 80%
      similarity, or more preferably greater than 90% similarity. In another preferred embodiment, the
      polynucleotide encodes the porcine α1(III) collagen amino acid sequence present in SEQ ID
10    NO:12, or fragments or variants thereof.

      Collagens from which nucleic acid sequence is not available may be obtained, by various methods
      known in the art, from cDNA libraries prepared from tissues believed to possess the type of
      collagen of interest and to express that collagen at a detectable level. For example, a cDNA
15    library could be constructed by obtaining polyadenylated mRNA from a cell line known to
      express the novel collagen, or a cDNA library previously made to the tissue/cell type could be
      used. The cDNA library is screened with appropriate nucleic acid probes, and/or the library is
      screened with suitable polyclonal or monoclonal antibodies that specifically recognize other
      collagens. Appropriate nucleic acid probes include oligonucleotide probes that encode known
20    portions of the novel collagen from the same or different species. Other suitable probes include,
      without limitation, oligonucleotides, cDNAs, or fragments thereof that encode the same or similar
      gene, and/or homologous genomic DNAs or fragments thereof. Screening the cDNA or genomic
      library with the selected probe may be accomplished using standard procedures known to those in
      the art. (See, e.g., Maniatis et al., *supra*.). Other means for identifying novel collagens involve
25    known techniques of recombinant DNA technology, such as by direct expression cloning or using
      the polymerase chain reaction (PCR) as described in U.S. Patent No. 4,683,195, or in, e.g.,
      Maniatis et al., *supra*, or Ausubel et al., *supra*.

      Altered polynucleotide sequences which may be used in accordance with the invention include
30    deletions, additions, or substitutions of different nucleotide residues resulting in a sequence that
      encodes the same or a functionally equivalent gene product. The gene product itself may contain
      deletions, additions, or substitutions of amino acid residues still resulting in a functionally equivalent
      polypeptide.

35    The nucleic acid sequences of the invention may be engineered in order to alter the coding sequence
      for a variety of ends including, but not limited to, alterations which modify processing and
      expression of the gene product. For example, alternative secretory signals may be substituted for the
      native secretory signal and/or mutations may be introduced using techniques which are well known
      in the art, e.g., site-directed mutagenesis, to insert new restriction sites, to alter glycosylation

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5 patterns, phosphorylati n, etc. In one embodiment, the polynucleotides of the present inventi n are
modified in the silent position of any triplet amino acid codon so as to better conform to the codon
preference of the particular host organism.

The polynucleotides of the present invention are further directed to sequences which encode variants
10 and fragments of the described animal collagens and gelatins. These amino acid fragments and
variants may be prepared by various methods known in the art for introducing appropriate nucleotide
and amino acid changes. Two important variables in the construction of amino acid variants are the
location of the mutation and the nature of the mutation. The amino acid variants of collagen are
preferably constructed by mutating the polynucleotide to give an amino acid sequence that does not
15 occur in nature. These amino acid alterations can be made at sites that differ in collagens from
different species (variable positions) or in highly conserved regions (constant regions). Sites at such
locations will typically be modified serially, e.g., by substituting first with conservative choices (e.g.,
hydrophobic amino acid to a different hydrophobic amino acid), and then with more distant choices
(e.g., hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be
20 made at the target site.

Amino acids are divided into groups based on the properties of their side chains (polarity, charge,
solubility, hydrophobicity, hydrophilicity, and/or the amphipatic nature): (1) hydrophobic (Leu,
Met, Ala, Ile), (2) neutral hydrophobic (Cys, Ser, Thr), (3) acidic (Asp, Glu), (4) weakly basic (Asn,
25 Gln, His), (5) strongly basic (Lys, Arg), (6) residues that influence chain orientation (Gly, Pro), and
(7) aromatic (Trp, Tyr, Phe). Conservative changes encompass variants of an amino acid position
that are within the same group as the "native" amino acid. Moderately conservative changes
encompass variants of an amino acid position that are in a group that is closely related to the
"native" amino acid (e.g., neutral hydrophobic to weakly basic). Non-conservative changes
30 encompass variants of an amino acid position that are in a group that is distantly related to the
"native" amino acid (e.g., hydrophobic to strongly basic or acidic).

Amino acid sequence deletions generally range from about 1 to 30 residues, preferably from about 1
to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or carboxyl-
35 terminal fusions ranging in length from one to one hundred or more residues, as well as
intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may
range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of
terminal insertions include the heterologous signal sequences necessary for secretion or for
intracellular targeting in different host cells.

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In another embodiment of the invention, a polynucleotide of the present invention may be ligated to a heterologous sequence to encode a fusion protein. For example, a fusion protein may be engineered to contain a cleavage site located between an α1(I) bovine collagen sequence of the present invention and the heterologous protein sequence, so that the α1(I) collagen may be cleaved

10    away from the heterologous moiety.

Polynucleotide variants can also be generated according to methods well-known in the art. In one method of the present invention, polynucleotides are changed via site-directed mutagenesis. This method uses oligonucleotide sequences that encode the polynucleotide sequence of the desired

15    amino acid variant, as well as a sufficient adjacent nucleotide on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, for example, Edelman et al. (1983) DNA 2:183. A versatile and efficient method for producing site-specific changes in a polynucleotide sequence is described in, e.g., by

20    Zoller and Smith (1982) Nucleic Acids Res. 10:6487-6500.

As known in the art, nucleic acid mutations do not necessarily alter the amino acid sequence encoded by a polynucleotide sequence while providing unique restriction sites useful for manipulation of the molecule. Thus, the modified molecule can be made up of a number of discrete regions, or D-

25    regions, flanked by unique restriction sites. These discrete regions of the molecule are herein referred to as cassettes. Molecules formed of multiple copies of a cassette are encompassed by the present invention. Recombinant or mutant nucleic acid molecules or cassettes, which provide desired characteristics, such as resistance to endogenous enzymes such as collagenase, are also encompassed by the present invention. (See, e.g., Maniatis et al., *supra*; and Ausubel et al., *supra*.)

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It will be appreciated by those skilled in the art that, as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding the polypeptides of the present invention, or functional equivalents thereof, some bearing minimal homology to the nucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates

35    each and every possible variation of nucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code.

35

5    The invention also encompasses production of polynucleotide sequences,  r fragments thereof,
     encoding the polypeptides of the present invention or functional equivalents thereof, entirely by
     synthetic chemistry.  After production, the synthetic sequence may be inserted into any of the many
     available expression vectors and cell systems using reagents that are well known in the art.
     Moreover, synthetic chemistry may be used to introduce mutations into a polynucleotide sequence
10   encoding a collagen or functional equivalents thereof.

     PCR may also be used to create variants of the present invention.  When small amounts of template
     nucleic acid are used as starting material, primer(s) that differs slightly in sequence from the
     corresponding region in the template nucleic acid can generate the desired amino acid variant.  PCR
15   amplification results in a population of product polynucleotide fragments that differ from the
     polynucleotide template encoding the collagen at the position specified by the primer.  The product
     fragments replace the corresponding region in the plasmid, creating the desired nucleic acid or amino
     acid variant.

20   Due to the inherent degeneracy of the genetic code, other polynucleotide sequences which encode
     substantially the same or functionally equivalent polypeptide sequences are encompassed by the
     present invention, and all degeneration variants and codon-optimized sequences are specifically
     contemplated.  Encoding polynucleotide sequences that are natural, synthetic, semi-synthetic, or
     recombinant may be used in the practice of the claimed invention.  Such polynucleotide sequences
25   include those capable of hybridizing to the appropriate polynucleotide sequence under stringent
     conditions.

     As naturally produced, collagens are structural proteins comprised of one or more collagen subunits
     which together form at least one triple-helical domain.  A variety of enzymes are utilized in order to
30   transform the collagen subunits into procollagen or other precursor molecules, and then into mature
     collagen.  Such enzymes include, for example, prolyl-4-hydroxylase, C-proteinase, N-proteinase,
     lysyl oxidase, lysyl hydroxylase, etc.

     Prolyl 4-hydroxylase is a $\alpha_2\beta_2$ tetramer, and plays a central role in the biosynthesis of all collagens,
35   4-hydroxyproline residues stabilize the folding of the newly synthesized polypeptide chains into
     stable triple-helical molecules.  (See, e.g., Prockop et al. (1995) Annu. Rev. Biochem. 64:403-434;
     Kivirikko et al. (1992) "Post-Translational Modifications of Proteins," pp. 1-51; and Kivirikko et al.
     (1989) FASEB J. 3:1609-1617.)  Additionally, the level of expression of type III collagen was lower
     in the absence of recombinant prolyl 4-hydroxylase than in its presence.  Human isoforms of prolyl

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5   4-hydroxylase have been cloned and characterized. (See, e.g., Helaakoski et al. (1995) Proc. Natl.
Acad. Sci. 92:4427-4431; U.S. Patent No. 5,928,922.)


Lysyl hydroxylase, an α2 homodimer, catalyzes the post-translational modification of collagen to
form hydroxylysine in collagens. See generally, Kivirikko et al. (1992) Post-Translational
10  Modifications of Proteins, Harding, J.J., and Crabbe, M.J.C., eds., CRC Press, Boca Raton, FL; and
Kivirikko (1995) Principles of Medical Biology, Vol. 3 Cellular Organelles and the Extracellular
Matrix, Bittar, E.E., and Bittar, N., eds., JAI Press, Greenwich, Great Britain. Isoforms of lysyl
hydroxylase have been cloned and identified. (See, e.g. Passoja et al. (1998) Proc. Natl. Acad. Sci.
95(18):10482-10486; and Valtavaara et al. (1997) J. Biol. Chem. 272(11):6831-6834.)
15

C-proteinase processes the assembled procollagen by cleaving off the C-terminal ends of the
procollagens that assist in assembly of, but are not part of, the triple helix of the collagen molecule.
(See, e.g., Kadler et al. (1987) J. Biol. Chem. 262:15969-15701; and Kadler et al. (1990) Ann. NY
Acad. Sci. 580:214-224.)
.20

N-proteinase processes the assembled procollagen by cleaving off the N-terminal ends of the
procollagens that assist in the assembly of, but are not part of, the collagen triple helix. (See, e.g.,
Hojima et al. (1994) J. Biol. Chem. 269:11381-11390.)


25  Lysyl oxidase is an extracellular copper enzyme that catalyzes the oxidative deamination of the α-
amino group in certain lysine and hydroxylysine residues to form a reactive aldehyde. These
aldehydes then undergo an aldol condensation to form aldols, which cross links collagen fibrils.
Information on the DNA and protein sequence of lysyl oxidase can found, for example, in Kivirikko
(1995), supra; Kagan (1994) Path. Res. Pract. 190: 910-919; Kenyon et al. (1993) J. Biol. Chem.
30  268(25):18435-18437; Wu et al. (1992) J. Biol. Chem. 267(34):24199-24206; Mariani et al. (1992)
Matrix 12(3):242-248; and Hamalainen et al. (1991) Genomics 11(3):508-516.


The nucleic acid sequences encoding a number of these post-translational enzymes have been
reported. (See, e.g., Vuori et al. (1992) Proc. Natl. Acad. Sci. USA 89:7467-7470; and Kessler et al.
35  (1996) Science 271:360-362. The nucleic acid sequences encoding various post-translational
enzymes may also be determined according to the methods generally described above and include
use of appropriate probes and nucleic acid libraries.

5    The recombinant animal gelatins f the present invention may be derived from animal collagens
     using a variety of procedures known in the art. (See, e.g., Veis, A. (1965) International Review of
     Connective Tissue Research, 3:113-200.) For example, a common feature of current processes is
     the denaturation of the secondary structure of the collagen protein, and in the majority of
     instances, an alteration in either the primary or tertiary structure of the collagen. Thus, the animal
10   collagens of the present invention can be processed using different procedures depending on the
     type of gelatin desired.

     Recombinant animal gelatins of the present invention can be derived from recombinantly produced
     collagen or procollagens or other collagenous polypeptides by a variety of methods known in the art.
15   For example, gelatin may be derived directly from cell mass or culture media by taking advantage of
     gelatin's solubility at elevated temperatures and its stability conditions of low or high pH, low or
     high salt concentration and high temperatures. Methods, processes, and techniques of producing
     gelatin compositions from collagen include denaturing the triple helical structure of the collagen
     utilizing detergents, heat, or various denaturing agents well known in the art. In addition, various
20   steps involved in the extraction of gelatin from animal or slaughterhouse sources, including
     treatment with lime or acids, heat extraction in aqueous solution, ion exchange chromatography,
     cross-flow filtration and various methods of drying can be used to derive the gelatin of the present
     invention from recombinant collagen.

25   **Expression**
     The present methods of producing animal collagens and gelatins can be applied in a variety of
     recombinant systems available to those in the art. A number of these recombinant systems are
     described herein, although it is to be understood that application of the present methods is not to be
     limited to the systems illustrated for example below.
30

     In order to express the recombinant animal collagens and gelatins of the present invention, or
     polypeptides from which the recombinant gelatins can be derived, the encoding polynucleotide is
     inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements
     for the transcription and translation of the inserted coding sequence, or in the case of an RNA viral
35   vector, the necessary elements for replication and translation.

     Methods which are well known to those skilled in the art can be used to construct expression vectors
     containing the polynucleotides of the invention and appropriate transcriptional/translational control
     signals. These methods include standard DNA cloning techniques, e.g., *in vitro* recombinant

5       techniques, synthetic techniques and *in vivo* recombination/genetic recombination. (See, for
        example, the techniques described in Maniatis et al., *supra*; and Ausubel et al., *supra*.)

        The expression elements of different systems vary in their strength and specificities. Depending on
        the host/vector system utilized, any of a number of suitable transcription and translation elements,
10      including constitutive and inducible promoters, may be used in the expression vector. For example,
        when cloning in bacterial systems, inducible promoters such as pL of bacteriophage γ plac, ptrp, ptac
        (ptrp-lac hybrid promoter) and the like may be used; when cloning in insect cell systems, promoters
        such as the baculovirus polyhedron promoter may be used; when cloning in plant cell systems,
        promoters derived from the genome of plant cells (e.g., heat shock promoters; the promoter for the
15      small subunit of RUBISCO; the promoter for the chlorophyll a/b binding protein) or from plant
        viruses (e.g., the 35S RNA promoter of CaMV; the coat protein promoter of TMV) may be used;
        when cloning in mammalian cell systems, promoters derived from the genome of mammalian cells
        (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the
        vaccinia virus 7.5 K promoter) may be used; when generating cell lines that contain multiple copies
20      of a collagen DNA, SV40-, BPV- and EBV-based vectors may be used with an appropriate
        selectable marker.

        Specific initiation signals may also be required for efficient translation of inserted sequences. These
        signals include the ATG initiation codon and adjacent sequences. In cases where the entire collagen
25      gene, including its own initiation codon and adjacent sequences, is inserted into the appropriate
        expression vector, no additional translational control signals may be needed. However, in cases
        where only a portion of a collagen coding sequence is inserted, exogenous translational control
        signals, including the ATG initiation codon, must be provided. Furthermore, the initiation codon
        must be in phase with the reading frame of the collagen coding sequence to ensure translation of the
30      entire insert. These exogenous translational control signals and initiation codons can be of a variety
        of origins, both natural and synthetic. The efficiency of expression may be enhanced by the
        inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (See, e.g.,
        Bittner et al. (1987) Methods in Enzymol. 153:516-544).

35      The polypeptides of the invention may be expressed as secreted proteins. When the engineered cells
        used for expression of the proteins are non-human host cells, it is often advantageous to replace the
        secretory signal peptide of the collagen protein with an alternative secretory signal peptide which is
        more efficiently recognized by the host cell's secretory targeting machinery. The appropriate
        secretory signal sequence is particularly important in obtaining optimal fungal expression of

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5    mammalian genes. For example, see, e.g., Brake et al. (1984) Proc. Natl. Acad. Sci. USA 81:4642.
     Other signal sequences for prokaryotic, yeast, fungi, insect or mammalian cells are well known in
     the art, and one of ordinary skill could easily select a signal sequence appropriate for the host cell of
     choice.

10   The vectors of this invention may autonomously replicate in the host cell, or may integrate into the
     host chromosome. Suitable vectors with autonomously replicating sequences are well known for a
     variety of bacteria, yeast, and various viral replications sequences for both prokaryotes and
     eukaryotes. Vectors may integrate into the host cell genome when they have a nucleic acid sequence
     homologous to a sequence found in the genomic DNA of the host cell.

15

     In one embodiment, the expression vectors of the present invention comprise a selectable marker,
     which encodes a product necessary for the host cell to grow and survive under certain conditions.
     Typical selection genes include genes encoding proteins that confer resistance to an antibiotic or
     other toxin (e.g., tetracycline, ampicillin, neomycin, methotrexate, etc.), proteins that complement an
20   auxotrophic requirement of the host cell, etc. Other examples of selection genes include the herpes
     simplex virus thymidine kinase (Wigler et al. (1977) Cell 11:223), hypoxanthine-guanine
     phosphoribosyltransferase (Szybalska et al. (1962) Proc. Natl. Acad. Sci. USA 48:2026), and
     adenine phosphoribosyltransferase (Lowy et al. (1980) Cell 22:817) genes, which can be employed
     in $tk^-$, $hgprt^-$, or $aprt^-$ cells, respectively.

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     Antimetabolite resistance can be used as the basis of selection, such as with the use of $dhfr$ which
     confers resistance to methotrexate; $gpt$, which confers resistance to mycophenolic acid; $neo$, which
     confers resistance to the aminoglycoside G-418; and $hygro$, which confers resistance to hygromycin.
     (See, e.g., Wigler et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567; O'Hare et al. (1981) Proc. Natl.
30   Acad. Sci. USA 78:1527; Mulligan et al. (1981) Proc. Natl. Acad. Sci. USA 78:2072; Colberre-
     Garapin et al. (1981) J. Mol. Biol. 150:1; and Santerre et al. (1984) Gene 30:147.) Additional
     selectable genes include $trpB$, which allows cells to utilize indole in place of tryptophan; $hisD$, which
     allows cells to utilize histinol in place of histidine; and $odc$ (ornithine decarboxylase) which confers
     resistance to the ornithine decarboxylase inhibitor, 2-(difluoromethyl)-DL-ornithine, DFMO. (See,
35   e.g., Hartman et al. (1988) Proc. Natl. Acad. Sci. USA 85:8047 and McConlogue L., In: Current
     Communications in Molecular Biology, Cold Spring Harbor Laboratory, Ed. (1987)).

     Elements necessary for the expression vectors of the invention include sequences for initiating
     transcription, e.g., promoters and enhancers. Promoters are untranslated sequences located upstream

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5    from the start codon of the structural gene that control the transcription of the nucleic acid under its
     control. Inducible promoters are promoters that alter their level of transcription initiation in response
     to a change in culture conditions, e.g., the presence or absence of a nutrient. One of skill in the art
     would know of a large number of promoters that would be recognized in host cells suitable for the
     present invention. These promoters are operably linked to the DNA encoding the collagen by
10   removing the promoter from its native gene and placing the collagen encoding DNA 3' of the
     promoter sequence.

     Promoters useful in the present invention include, but are not limited to, the lactose promoter, the
     alkaline phosphatase promoter, the tryptophan promoter, hybrid promoters such as the tac promoter,
15   promoter for 3-phosphoglycerate kinase, other glycolytic enzyme promoters (hexokinase, pyruvate
     decarboxylase, phophofructosekinase, glucose-6-phosphate isomerase, etc.), the promoter for alcohol
     dehydrogenase, the metallothionein promoter, the maltose promoter, the galactose promoter,
     promoters from the viruses polyoma, fowlpox, adenovirus, bovine papilloma virus, avian sarcoma
     virus, cytomegalovirus, retroviruses, SV40, and promoters from target eukaryotes including the
20   glucoamylase promoter from *Aspergillus*, the actin promoter or an immunoglobin promoter from a
     mammal, and native collagen promoters. (See, e.g., de Boer et al. (1983) Proc. Natl. Acad. Sci. USA
     80:21-25; Hitzeman et al. (1980) J. Biol. Chem. 255:2073; Fiers et al. (1978) Nature 273:113;
     Mulligan and Berg (1980) Science 209:1422-1427; Pavlakis et al. (1981) Proc. Natl. Acad. Sci. USA
     78:7398-7402; Greenway et al. (1982) Gene 18:355-360; Gray et al. (1982) Nature 295:503-508;
25   Reyes et al. (1982) Nature 297:598-601; Canaani and Berg (1982) Proc. Natl. Acad. Sci. USA
     79:5166-5170; Gorman et al. (1982) Proc. Natl. Acad. Sci. USA 79:6777-6781; and Nunberg et al.
     (1984) Mol. and Cell. Biol. 11(4):2306-2315.)

     Transcription of the coding sequence from the promoter is often increased by inserting an enhancer
30   sequence in the vector. Enhancers are cis-acting elements, usually about from 10 to 300 bp, that act
     to increase the rate of transcription initiation at a promoter. Many enhancers are known for both
     eukaryotes and prokaryotes, and one of ordinary skill could select an appropriate enhancer for the
     host cell of interest. (See, e.g., Yaniv (1982) Nature 297:17-18.)

35   In addition, a host cell strain may be chosen which modulates the expression of the inserted
     sequences, or modifies and processes the gene product in the specific fashion desired. Such
     modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be
     important for the function of the protein. Different host cells have characteristic and specific
     mechanisms for the post-translational processing and modification of proteins. Appropriate cells

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5     lines or host systems can be chosen to ensure the correct modification and processing of the foreign
      protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper
      processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be
      used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS,
      MDCK, 293, WI38, etc. Additionally, host cells may be engineered to express various enzymes to
10    ensure the proper processing of the encoded polypeptide. For example, the gene for prolyl 4-
      hydroxylase may be co-expressed with a polynucleotide encoding a collagen or fragments or variants
      thereof to achieve proper hydroxylation.

      For long-term, high-yield production of recombinant proteins, stable expression is preferred. For
15    example, cell lines which stably express the collagens of the invention may be engineered. Rather
      than using expression vectors which contain viral origins of replication, host cells can be
      transformed with collagen encoding DNA controlled by appropriate expression control elements
      (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a
      selectable marker. Following the introduction of foreign DNA, engineered cells may be allowed to
20    grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable
      marker in the recombinant plasmid confers resistance to the selection and allows cells to stably
      integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and
      expanded into cell lines. Thus, the present methods may advantageously be used to engineer cell
      lines which express a desired animal collagen or fragments or variants thereof.

25

      For example, expression of the present polypeptides driven by the galactose promoters can be
      induced by growing the culture on a non-repressing, non-inducing sugar so that very rapid induction
      follows addition of galactose; by growing the culture in glucose medium and then removing the
      glucose by centrifugation and washing the cells before resuspension in galactose medium; and by
30    growing the cells in medium containing both glucose and galactose so that the glucose is
      preferentially metabolized before galactose-induction can occur.

      The vectors expressing the polypeptides of the present invention, and the vectors expressing
      polynucleotides encoding any post-translational enzymes desired may be introduced into host cells
35    to produce the encoded polypeptides, using techniques known to one of skill in the art. For example,
      host cells are transfected or infected or transformed with the above-described expression vectors, and
      cultured in nutrient media appropriate for selecting transductants or transformants containing the
      collagen encoding vector. Cell transfection can be carried out by a variety of methods available to
      those of skill in the art, such as, for example, by calcium phosphate precipitation, electroporation,

5    and lipofection techniques. (See, e.g., Maniatis et al., *supra*, Ohta T. (1996) Nippon Rinsho
     54(3):757-764; Trotter and Wood (1996) Mol Biotechnol 6(3):329-334; Mann and King (1989) J
     Gen Virol 70:3501-3505; and Hartig et al. (1991) Biotechniques 11(3):310.)

     In one embodiment, the present invention provides a method in which more than one of the
10   expression vectors encoding for the polypeptides of the present invention are inserted into cells, so
     that, e.g., trimeric collagens can be synthesized. For example, in one method of producing animal
     collagen according to the present invention, cells may be co-infected, co-transfected, or co-
     transformed with a first vector comprising a polynucleotide encoding a porcine α1(I) collagen, a
     second vector comprising a polynucleotide encoding a porcine α2(I) collagen, and third and fourth
15   vectors comprising polynucleotides encoding the α subunit and the β subunit of prolyl 4-hydroxylase
     under conditions suitable for expression of the polypeptides and a fully hydroxylated, heterotrimeric
     porcine collagen.

     In another method of the present invention, production of homotrimeric collagen is contemplated.
20   For example, in the production of bovine collagen type III, cells may be co-infected, co-transfected,
     or co-transformed with a first vector comprising a polynucleotide encoding a bovine α1(III)
     collagen, a second vector comprising a polynucleotide encoding an α subunit of prolyl 4-
     hydroxylase, and a third vector comprising a polynucleotide encoding a β subunit of prolyl 4-
     hydroxylase. Other animal collagens, including mammalian collagens such as porcine, ovine, and
25   equine collagens, and non-mammalian animal collagens, such as chicken and piscine collagen, may
     be produced using the same or similar co-expression methods and techniques, and variations thereof
     within the level of skill in the art.

     Host cells containing coding sequence and expressing the biologically active gene product may be
30   identified by any number of techniques known in the art. Such techniques include, for example,
     detecting the formation of nucleic acid hybridization complexes, detecting the presence or absence of
     marker gene functions assessing the level of transcription as measured by the expression of mRNA
     transcripts in the host cell, and detecting gene product as measured by immunoassay or by biological
     activity.
35
     In the first approach, the presence of the present polynucleotide can be detected by, for example,
     detection of DNA-DNA or DNA-RNA hybridization complexes, or by amplification using probes
     comprising nucleotide sequences homologous to the animal collagen coding sequence, or portions,

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5      or derivatives thereof. Amplification-based assays involve the use of oligonucleotides or oligomers
       based on sequences homologous to the coding sequence of interest to detect transformants
       containing the encoding polynucleotides.

       In the second approach, the recombinant expression vector/host system is identified and selected
10     based upon the presence or absence of certain marker gene functions (e.g., thymidine kinase activity,
       resistance to antibiotics, resistance to methotrexate, transformation phenotype, occlusion body
       formation in baculovirus, etc.). For example, if the coding sequence is inserted within a marker gene
       sequence of the vector, recombinant cells containing coding sequence can be identified by the
       absence of the marker gene function. Alternatively, a marker gene can be placed in tandem with the
15     coding sequence under the control of the same or different promoter used to control the expression
       of the coding sequence. Expression of the marker in response to induction or selection indicates
       expression of the coding sequence.

       In the third approach, transcriptional activity of the coding region can be assessed by hybridization
20     assays. For example, RNA can be isolated and analyzed by northern blot using a probe homologous
       to the coding sequence or particular portions thereof. Alternatively, total nucleic acids of the host
       cell may be extracted and assayed for hybridization to such probes.

       In the fourth approach, the expression of a protein product can be assessed immunologically, for
25     example by Western blots, immunoassays such as radioimmuno-precipitation, enzyme-linked
       immunoassays, and the like.

       In one embodiment, the animal collagens of the present invention are secreted into the culture
       medium, and can be purified to homogeneity by various methods known in the art, for example, by
30     chromatography. In one embodiment, recombinant animal collagens of the present invention are
       purified by size exclusion chromatography. However, other purification techniques known in the art
       can also be used, including ion exchange chromatography, and reverse-phase chromatography. (See,
       e.g., Maniatis et al., *supra*, Ausubel et al., *supra*, and Scopes (1994) Protein Purification: Principles
       and Practice, Springer-Verlag New York, Inc., NY.)

35
       The present methods can be used in, although are not limited in application to, the expression
       systems listed below.

5      Prokaryotic

In prokaryotic systems, such as bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the expressed polypeptide. For example, when large quantities of the animal collagens and gelatins of the invention are to be produced, such as for the generation of antibodies, vectors which direct the expression of high levels
10      of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al. (1983) EMBO J. 2:1791), in which the coding sequence may be ligated into the vector in frame with the lac Z coding region so that a hybrid AS-lac Z protein is produced; pIN vectors (Inouye et al. (1985) Nucleic Acids Res. 13:3101-3109 and Van Heeke et al. (1989) J. Biol. Chem. 264:5503-5509); and the like. pGEX
15      vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety.

20

Yeast

In one embodiment, the present polypeptides are produced in a yeast expression system. In yeast, a number of vectors containing constitutive or inducible promoters known in the art may be used. (See, e.g., Ausubel et al., *supra*, Vol. 2, Chapter 13; Grant et al. (1987) Expression and Secretion
25      Vectors for Yeast, in Methods in Enzymology, Ed. Wu & Grossman, Acad. Press, N.Y. 153:516-544; Glover (1986) DNA Cloning, Vol. II, IRL Press, Wash., D.C., Ch. 3; Bitter (1987) Heterologous Gene Expression in Yeast, in Methods in Enzymology, Eds. Berger & Kimmel, Acad. Press, N.Y. 152:673-684; and The Molecular Biology of the Yeast Saccharomyces, Eds. Strathern et al., Cold Spring Harbor Press, Vols. I and II (1982).)

30

Polypeptides of the present invention can be expressed using host cells, for example, from the yeast *Saccharomyces cerevisiae*. This particular yeast can be used with any of a large number of expression vectors. Commonly employed expression vectors are shuttle vectors containing the $2\mu$ origin of replication for propagation in yeast and the Col E1 origin for *E. coli*, for efficient
35      transcription of the foreign gene. A typical example of such vectors based on $2\mu$ plasmids is pWYG4, which has the $2\mu$ ORI-STB elements, the GAL1-10 promoter, and the $2\mu$ D gene terminator. In this vector, an Ncol cloning site is used to insert the gene for the polypeptide to be expressed, and to provide the ATG start codon. Another expression vector is pWYG7L, which has intact 2α ORI, STB, REP1 and REP2, and the GAL1-10 promoter, and uses the FLP terminator. In

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5      this vector, the encoding polynucleotide is inserted in the polylinker with its 5' ends at a *BamHI* or
       *Ncol* site. The vector containing the inserted polynucleotide is transformed into *S. cerevisiae* either
       after removal of the cell wall to produce spheroplasts that take up DNA on treatment with calcium
       and polyethylene glycol or by treatment of intact cells with lithium ions.

10     Alternatively, DNA can be introduced by electroporation. Transformants can be selected, for
       example, using host yeast cells that are auxotrophic for leucine, tryptophane, uracil, or histidine
       together with selectable marker genes such as LEU2, TRP1, URA3, HIS3, or LEU2-D.

       In one embodiment of the invention, the present polynucleotides are introduced into host cells from
15     the yeast *Pichia*. Species of non-*Saccharomyces* yeast such as *Pichia pastoris* appear to have special
       advantages in producing high yields of recombinant protein in scaled up procedures. Additionally, a
       *Pichia* expression kit is available from Invitrogen Corporation (San Diego, CA).

       There are a number of methanol responsive genes in methylotrophic yeasts such as *Pichia pastoris*,
20     the expression of each being controlled by methanol responsive regulatory regions, also referred to
       as promoters. Any of such methanol responsive promoters are suitable for use in the practice of the
       present invention. Examples of specific regulatory regions include the AOX1 promoter, the AOX2
       promoter, the dihydroxyacetone synthase (DAS), the P40 promoter, and the promoter for the catalase
       gene from *P. pastoris*, etc.

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       In other embodiments, the present invention contemplates the use of the methylotrophic yeast
       *Hansenula polymorpha*. Growth on methanol results in the induction of key enzymes of the
       methanol metabolism, such as MOX (methanol oxidase), DAS (dihydroxyacetone synthase), and
       FMHD (formate dehydrogenase). These enzymes can constitute up to 30-40% of the total cell
30     protein. The genes encoding MOX, DAS, and FMDH production are controlled by strong promoters
       induced by growth on methanol and repressed by growth on glucose. Any or all three of these
       promoters may be used to obtain high-level expression of heterologous genes in *H. polymorpha*.
       Therefore, in one aspect of the invention, a polynucleotide encoding animal collagen or fragments or
       variants thereof is cloned into an expression vector under the control of an inducible *H. polymorpha*
35     promoter. If secretion of the product is desired, a polynucleotide encoding a signal sequence for
       secretion in yeast is fused in frame with the polynucleotide. In a further embodiment, the expression
       vector preferably contains an auxotrophic marker gene, such as URA3 or LEU2, which may be used
       to complement the deficiency of an auxotrophic host.

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5      The expression vector is then used to transform *H. polymorpha* host cells using techniques known to
       those of skill in the art. A useful feature of *H. polymorpha* transformation is the spontaneous
       integration of up to 100 copies of the expression vector into the genome. In most cases, the
       integrated polynucleotide forms multimers exhibiting a head-to-tail arrangement. The integrated
       foreign polynucleotide has been shown to be mitotically stable in several recombinant strains, even
10     under non-selective conditions. This phenomena of high copy integration further adds to the high
       productivity potential of the system.


       Fungi
       Filamentous fungi may also be used to produce the present polypeptides. Vectors for expressing
15     and/or secreting recombinant proteins in filamentous fungi are well known, and one of skill in the art
       could use these vectors to express the recombinant animal collagens of the present invention.


       Plant
       In one aspect, the present invention contemplates the production of animal collagens and gelatins in
20     plants and plant cells. In cases where plant expression vectors are used, the expression of sequences
       encoding the collagens of the invention may be driven by any of a number of promoters. For
       example, viral promoters such as the 35S RNA and 19S RNA promoters of CaMV (Brisson et al.
       (1984) Nature 310:511-514), or the coat protein promoter of TMV (Takamatsu et al. (1987) EMBO
       J. 6:307-311) may be used; alternatively, plant promoters such as the small subunit of RUBISCO
25     (Coruzzi et al. (1984) EMBO J. 3:1671-1680; Broglie et al. (1984) Science 224:838-843) or heat
       shock promoters, e.g., soybean hsp17.5-E or hsp17.3-B (Gurley et al. (1986) Mol. Cell. Biol. 6:559-
       565) may be used. These constructs can be introduced into plant cells by a variety of methods
       known to those of skill in the art, such as by using Ti plasmids, Ri plasmids, plant virus vectors,
       direct DNA transformation, microinjection, electroporation, etc. For reviews of such techniques see,
30     for example, Weissbach & Weissbach, Methods for Plant Molecular Biology, Academic Press, NY,
       Section VIII, pp. 421-463 (1988); Grierson & Corey, Plant Molecular Biology, 2d Ed., Blackie,
       London, Ch. 7-9 (1988); Transgenic Plants: A Production System for Industrial and Pharmaceutical
       Proteins, Owen and Pen eds., John Wiliey & Sons, 1996; Transgenic Plants, Galun and Breiman eds,
       Imperial College Press, 1997; and Applied Plant Biotechnology, Chopra, Malik, and Bhat eds.,
35     Science Publishers, Inc., 1999.


       Plant cells do not naturally produce sufficient amounts of post-translational enzymes to efficiently
       produce stable collagen. Therefore, the present invention provides that, where hydroxylation is
       desired, plant cells used to express the present animal collagens are supplemented with the necessary

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5    post-translational enzymes to sufficiently produce stable collagen. In a preferred embodiment of the
present invention, the post-translational enzyme is prolyl 4-hydroxylase.

Methods of producing the present animal collagens or gelatins in plant systems may be achieved by
providing a biomass from plants or plant cells, wherein the plants or plant cells comprise at least one
10   coding sequence is operably linked to a promoter to effect the expression of the polypeptide, and the
polypeptide is then extracted from the biomass. Alternatively, the polypeptide can be non-extracted,
i.e., expressed into the endosperm, etc.

Plant expression vectors and reporter genes are generally known in the art. (See, e.g., Gruber et
15   al. (1993) in Methods of Plant Molecular Biology and Biotechnology, CRC Press.) Typically, the
expression vector comprises a nucleic acid construct generated, for example, recombinantly or
synthetically, and comprising a promoter that functions in a plant cell, wherein such promoter is
operably linked to a nucleic acid sequence encoding an animal collagen or fragments or variants
thereof, or a post-translational enzyme important to the biosynthesis of collagen.
20

Promoters drive the level of protein expression in plants. To produce a desired level of protein
expression in plants, expression may be under the direction of a plant promoter. Promoters
suitable for use in accordance with the present invention are generally available in the art. (See,
e.g., PCT Publication No. WO 91/19806.) Examples of promoters that may be used in
25   accordance with the present invention include non-constitutive promoters or constitutive
promoters. These promoters include, but are not limited to, the promoter for the small subunit of
ribulose-1,5-bis-phosphate carboxylase; promoters from tumor-inducing plasmids of
*Agrobacterium tumefaciens*, such as the RUBISCO nopaline synthase (NOS) and octopine
synthase promoters; bacterial T-DNA promoters such as *mas* and *ocs* promoters; and viral
30   promoters such as the cauliflower mosaic virus (CaMV) 19S and 35S promoters or the figwort
mosaic virus 35S promoter.

The polynucleotide sequences of the present invention may be under the transcriptional control of
a constitutive promoter, directing expression of the collagen or post-translational enzyme in most
35   tissues of a plant. In one embodiment, the polynucleotide sequence is under the control of the
cauliflower mosaic virus (CaMV) 35S promoter. The double-stranded caulimorvirus family has
provided the single most important promoter expression for transgene expression in plants, in
particular, the 35S promoter. (See, e.g., Kay et al. (1987) Science 236:1299.) Additional
promoters from this family such as the figwort mosaic virus promoter, etc., have been described

5       in the art, and may also be used in accordance with the present invention. (See, e.g., Sanger et al.
        (1990) Plant Mol. Biol. 14:433-443; Medberry et al. (1992) Plant Cell 4:195-192; and Yin and
        Beachy (1995) Plant J. 7:969-980.)

        The promoters used in the polynucleotide constructs of the present invention may be modified, if
10      desired, to affect their control characteristics. For example, the CaMV promoter may be ligated to
        the portion of the RUBISCO gene that represses the expression of RUBISCO in the absence of
        light, to create a promoter which is active in leaves, but not in roots. The resulting chimeric
        promoter may be used as described herein.

15      Constitutive plant promoters having general expression properties known in the art may be used
        with the expression vectors of the present invention. These promoters are abundantly expressed
        in most plant tissues and include, for example, the actin promoter and the ubiquitin promoter.
        (See, e.g., McElroy et al. (1990) Plant Cell 2:163-171; and Christensen et al. (1992) Plant Mol.
        Biol. 18:675-689.)

20

        Alternatively, the polypeptide of the present invention may be expressed in a specific tissue, cell
        type, or under more precise environmental conditions or developmental control. Promoters
        directing expression in these instances are known as inducible promoters. In the case where a
        tissue-specific promoter is used, protein expression is particularly high in the tissue from which
25      extraction of the protein is desired. Depending on the desired tissue, expression may be targeted
        to the endosperm, aleurone layer, embryo (or its parts as scutellum and cotyledons), pericarp,
        stem, leaves tubers, roots, etc. Examples of known tissue-specific promoters include the tuber-
        directed class I patatin promoter, the promoters associated with potato tuber ADPGPP genes, the
        soybean promoter of β-conglycinin (7S protein) which drives seed-directed transcription, and
30      seed-directed promoters from the zein genes of maize endosperm. (See, e.g., Bevan et al. (1986)
        Nucleic Acids Res. 14: 4625-38; Muller et al. (1990) Mol. Gen. Genet. 224:136-46; Bray (1987)
        Planta 172:364-370; and Pedersen et al. (1982) Cell 29:1015-26.)

        In a preferred embodiment, the present polypeptides are produced in seed by way of seed-based
35      production techniques using, for example, canola, corn, soybeans, rice and barley seed. In such a
        process, for example, the product is recovered during seed germination. (See, e.g., PCT
        Publication Numbers WO 9940210; WO 9916890; WO 9907206; U.S. Patent No. 5,866,121; U.S.
        Patent No. 5,792,933; and all references cited therein.)

                                                        49

5    Promoters that may be used to direct the expression of the polypeptides may be heterologous or
     non-heterologous. These promoters can also be used to drive expression of antisense nucleic
     acids to reduce, increase, or alter concentration and composition of the present animal collagens
     in a desired tissue.

10   Other modifications that may be made to increase and/or maximize transcription of the present
     polypeptides in a plant or plant cell are standard and known to those in the art. For example a
     vector comprising a polynucleotide sequence encoding a recombinant animal collagen or gelatin,
     or a polypeptide from which the recombinant animal gelatin may be derived, or a fragment or
     variant thereof, operably linked to a promoter may further comprise at least one factor that
15   modifies the transcription rate of collagen or related post-translational enzymes, including, but not
     limited to, peptide export signal sequence, codon usage, introns, polyadneylation, and
     transcription termination sites. Methods of modifying constructs to increase expression levels in
     plants are generally known in the art. (See, e.g. Rogers et al. (1985) J. Biol. Chem. 260:3731; and
     Cornejo et al. (1993) Plant Mol Biol 23:567-58.) In engineering a plant system that affects the
20   rate of transcription of the present collagens and related post-translational enzymes, various
     factors known in the art, including regulatory sequences such as positively or negatively acting
     sequences, enhancers and silencers, as well as chromatin structure can affect the rate of
     transcription in plants. The present invention provides that at least one of these factors may be
     utilized in expressing the recombinant animal collagens and gelatins described herein.

25
     The vectors comprising the present polynucleotides will typically comprise a marker gene which
     confers a selectable phenotype on plant cells. Usually, the selectable marker gene will encode
     antibiotic resistance, with suitable genes including at least one set of genes coding for resistance
     to the antibiotic spectinomycin, the streptomycin phophotransferase (SPT) gene coding for
30   streptomycin resistance, the neomycin phophotransferase (NPTH) gene encoding kanamycin or
     geneticin resistance, the hygromycin resistance, genes coding for resistance to herbicides which
     act to inhibit the action of acetolactate synthase (ALS), in particular, the sulfonylurea-type
     herbicides (e.g., the acetolactate synthase (ALS) gene containing mutations leading to such
     resistance in particular the S4 and/or Hra mutations), genes coding for resistance to herbicides
35   which act to inhibit action of glutamine synthase, such as phophinothricin or basta (e.g. the bar
     gene), or other similar genes known in the art. The bar gene encodes resistance to the herbicide
     basta, the *nptII* gene encodes resistance to the antibiotics kanamycin and geneticin, and the ALS
     gene encodes resistance to the herbicide chlorsulfuron.

5      Typical vectors useful for expression of foreign genes in plants are well known in the art,
       including, but not limited to, vectors derived from the tumor-inducing (Ti) plasmid of
       *Agrobacterium tumefaciens*. These vectors are plant integrating vectors, that upon
       transformation, integrate a portion of the DNA into the genome of the host plant. (See, e.g.,
       Rogers et al. (1987) Meth. In Enzymol. 153:253-277; Schardl et al. (1987) Gene 61:1-11; and
10     Berger et al., Proc. Natl. Acad. Sci. U.S.A. 86:8402-8406.)


       Vectors comprising sequences encoding the present polypeptides and vectors comprising post-
       translational enzymes or subunits thereof may be co-introduced into the desired plant. Procedures
       for transforming plant cells are available in the art, for example, direct gene transfer, *in vitro*
15     protoplast transformation, plant virus-mediated transformation, liposome-mediated
       transformation, microinjection, electroporation, *Agrobacterium* mediated transformation, and
       particle bombardment. (See, e.g., Paszkowski et al. (1984) EMBO J. 3:2717-2722; U.S. Patent
       No. 4,684,611; European Application No. 0 67 553; U.S. Patent No. 4,407,956; U.S. Patent No.
       4,536,475; Crossway et al. (1986) Biotechniques 4:320-334; Riggs et al. (1986) Proc. Natl. Acad.
20     Sci USA 83:5602-5606; Hinchee et al. (1988) Biotechnology 6:915-921; and U.S. Patent No.
       4,945,050.) Standard methods for the transformation of, e.g., rice, wheat, corn, sorghum, and
       barley are described in the art. (See, e.g., Christou et al. (1992) Trends in Biotechnology 10: 239
       and Lee et al. (1991) Proc. Nat'l Acad. Sci. USA 88:6389.) Wheat can be transformed by
       techniques similar to those employed for transforming corn or rice. Furthermore, Casas et al.
25     (1993) Proc. Nat'l Acad. Sci. USA 90:11212, describe a method for transforming sorghum, while
       Wan et al. (1994) Plant Physiol. 104: 37, teach a method for transforming barley. Suitable
       methods for corn transformation are provided by Fromm et al. (1990) Bio/Technology 8:833 and
       by Gordon-Kamm et al., *supra*.


30     Additional methods that may be used to generate plants that produce animal collagens of the
       present invention are well established in the art. (See, e.g., U.S. Patent No. 5,959,091; U.S. Patent
       No. 5,859,347; U.S. Patent No. 5,763,241; U.S. Patent No. 5,659,122; U.S. Patent No. 5,593,874;
       U.S. Patent No. 5,495,071; U.S. Patent No. 5,424,412; U.S. Patent No. 5,362,865; U.S. Patent No.
       5,229,112; U.S. Patent No. 5,981,841; U.S. Patent No. 5,959,179; U.S. Patent No. 5,932,439; U.S.
35     Patent No. 5,869,720; U.S. Patent No. 5,804,425; U.S. Patent No. 5,763,245; U.S. Patent No.
       5,716,837; U.S. Patent No. 5,689,052; U.S. Patent No. 5,633,435; U.S. Patent No. 5,631,152; U.S.
       Patent No. 5,627,061; U.S. Patent No. 5,602,321; U.S. Patent No. 5,589,612; U.S. Patent No.
       5,510,253; U.S. Patent No. 5,503,999; U.S. Patent No. 5,378,619; U.S. Patent No. 5,349,124; U.S.
       Patent No. 5,304,730; U.S. Patent No. 5,185,253; U.S. Patent No. 4,970,168; European

5   Publication No. EPA 00709462; European Publication No. EPA 00578627; European Publication
    No. EPA 00531273; European Publication No. EPA 00426641; PCT Publication No. WO
    99/31248; PCT Publication No. WO 98/58069; PCT Publication No. WO 98/45457; PCT
    Publication No. WO 98/31812; PCT Publication No. WO 98/08962; PCT Publication No. WO
    97/48814; PCT Publication No. WO 97/30582; and PCT Publication No. WO 9717459.)

10

Insect

Another alternative expression system used in accordance with the present methods is an insect
system. Baculoviruses are very efficient expression vectors for the large scale production of various
recombinant proteins in insect cells. The methods as described in, for example, Luckow et al. (1989)
15  Virology 170:31-39 and Gruenwald, S. and Heitz, J. (1993) Baculovirus Expression Vector System:
Procedures & Methods Manual, Pharmingen, San Diego, CA, can be employed to construct
expression vectors containing a collagen coding sequence for the collagens of the invention and the
appropriate transcriptional/translational control signals. For example, recombinant production of
proteins can be achieved in insect cells, by infection of baculovirus vectors encoding the
20  polypeptide. In one aspeect of the present invention, production of recombinant polypeptides with
stable triple helices can involve the co-infection of insect cells with three baculoviruses, one
encoding the animal collagen to be expressed and one each encoding the α subunit and β subunit of
prolyl 4-hydroxylase. This insect cell system allows for production of recombinant proteins in large
quantities. In one such system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used
25  as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Coding
sequence for the polypeptides of the invention may be cloned into non-essential regions (for example
the polyhedron gene) of the virus and placed under control of an AcNPV promoter (for example, the
polyhedron promoter). Successful insertion of a coding sequence will result in inactivation of the
polyhedron gene and production of non-occluded recombinant virus (i.e., virus lacking the
30  proteinaceous coat coded for by the polyhedron gene). These recombinant viruses are then used to
infect *Spodoptera frugiperda* cells in which the inserted gene is expressed. (See, e.g., Smith et aL
(1983) J. Virol. 46:584; and U.S. Patent No. 4,215,051). Further examples of this expression system
may be found in, for example, Ausubel et al., *supra*.


35  Animal

In animal host cells, a number of expression systems may be utilized. In cases where an
adenovirus is used as an expression vector, polynucleotide sequences of the present invention may
be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and
tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by

5  *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g.,
region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the
encoded polypeptides in infected hosts. (See, e.g., Logan & Shenk, Proc. Natl. Acad. Sci. USA
81:3655-3659 (1984)). Alternatively, the vaccinia 7.5 K promoter may be used. (See, e.g.,
Mackett et al. (1982) Proc. Natl. Acad. Sci. USA 79:7415-7419; Mackett et al. (1982) J. Virol.

10  49:857-864; and Panicali et al. (1982) Proc. Natl. Acad. Sci. USA 79:4927-4931.


   A preferred expression system in mammalian host cells is the Semliki Forest virus. Infection of
mammalian host cells, for example, baby hamster kidney (BHK) cells and Chinese hamster ovary
(CHO) cells can yield very high recombinant expression levels. Semliki Forest virus is a

15  preferred expression system as the virus has a broad host range such that infection of mammalian
cell lines will be possible. More specifically, it is expected that the use of the Semliki Forest virus
can be used in a wide range of hosts, as the system is not based on chromosomal intergration, and
therefore will be a quick way of obtaining modifications of the recombinant animal collagens in
studies aiming at identifying structure-function relationships and testing the effects of various

20  hybrid molecules. Methods for constructing Semliki Forest virus vectors for expression of
exogenous proteins in mammalian host cells are described in, for example, Olkkonen et al. (1994)
Methods Cell Biol 43:43-53.


   Transgenic animals may also be used to express the polypeptides of the present invention. Such

25  systems can be constructed by operably linking the polynucleotide of the invention to a promoter,
along with other required or optional regulatory sequences capable of effecting expression in
mammary glands. Likewise, required or optional post-translational enzymes may be produced
simultaneously in the target cells employing suitable expression systems. Methods of using
transgenic animals to recombinantly produce proteins are known in the art. (See, e.g., U.S. Patent

30  No. 4,736,866; U.S. Patent No. 5,824,838; U.S. Patent No. 5,487,992; and U.S. Patent No.
5,614,396.)


### Uses of Collagens and Gelatins

   The recombinant collagens and gelatins of the present invention are useful in a variety of

35  applications. Collagen is widely used in numerous applications in the medical, pharmaceutical,
food, and cosmetic industries. For example, collagen is an important component of arterial
sealants, bone grafts, drug delivery systems, dermal implants, hemostats, and incontinence
implants. In treatments for autoimmune disorders such as rheumatoid arthritis, collagen has been
evaluated in trials for its potential to induce oral-tolerance. Collagen is also applied in food

5    products such as sausage casings, and other collagen-based casings derived from, for example, porcine, bovine, and ovine sources. In health and beauty applications, collagen can be found, for example, in cosmetics or facial and skin products such as moisturizers. To date, various collagens used in various applications are derived from animal sources using enzymatic and chemical processes. For example, commercially available bovine collagen is isolated from bovine tissues

10    and bones, and is comprised of a mixture of primarily types I and III collagen. This form of collagen is also used as an injectable device in humans.

Gelatin appears in the manufacture or as a component of various pharmaceutical and medical products and devices, including pharmaceutical stabilizers, e.g., drug and vaccine, plasma

15    extenders, sponges, hard and soft gelatin capsules, suppositories, etc. Gelatin's film-forming capabilities are employed in various film coating systems designed specifically for pharmaceutical oral solid dosage forms, including controlled release capsules and tablets.

Gelatin in various edible forms has long been used in the food and beverage industries. Gelatin

20    serves as an emulsifier and thickener in various whipped toppings, as well as in soups and sauces. Gelatin is used as a flocculating agent in clarifying and fining various beverages, including wines and fruit juices. Gelatin is used in various low and reduced fat products as a thickener and stabilizer, and appears elsewhere as a fat substitute. Gelatin is also widely used in micro-encapsulation of flavorings, colors, and vitamins. Gelatin can also be used as a protein

25    supplement in various high energy and nutritional beverages and foods, such as those prevalent in the weight-loss and athletic industries. As a film-former, gelatin is used in coating fruits, meats, deli items, and in various confectionery products, including candies and gum, etc.

In the cosmetics industry, gelatin appears in a variety of hair care and skin care products. Gelatin

30    is used as a thickener and bodying agent in a number of shampoos, mousses, creams, lotions, face masks, lipsticks, manicuring solutions and products, and other cosmetic devices and applications. Gelatin is also used in the cosmetics industry in micro-encapsulation and packaging of various products.

35    Gelatin is used in a wide range of industrial applications. For example, gelatin is widely used as a glue and adhesive in various manufacturing processes. Gelatin can be used in various adhesive and gluing formulations, such as in the manufacture of remoistenable gummed paper packaging tapes, wood gluing, paper bonding of various grades of box boards and papers, and in various applications which provide adhesive surfaces which can be reactivated by remoistening.

5      Gelatin serves as a light-sensitive coating in various electronic devices and is used as a photoresist

       base in various photolithographic processes, for example, in color television and video camera

       manufacturing. In semiconductor manufacturing, gelatin is used in constructing lead frames and

       in the coating of various semiconductor elements. Gelatin is used in various printing processes

10     and in the manufacturing of special quality papers, such as that used in bond and stock

       certificates, etc.


       Gelatin is used in a variety of photographic applications, e.g., as a carrier for various active

       components in photographic solutions, including solutions used in X-ray and photographic film

15     development. Gelatin, long used in various photoengraving techniques, is also included as a

       component of various types of film, and is heavily used in silver halide chemistry in various

       layers of film and paper products. Silver gelatin film appears in the form of microfiche film and

       in other forms of information storage. Gelatin is used as a self-sealing element of various films,

       etc.

20

       Gelatin has also been a valuable substance for use in various laboratory applications. For

       example, gelatin can be used in various cell culture applications, providing a suitable surface for

       cell attachment and growth, e.g., plate or flask coating, or providing a surface for cell attachment

       and growth. Hydrolyzed or low gel strength gelatin is used as a biological buffer in various

25     processes, for example, in coating and blocking solutions used in assays such as enzyme-linked

       immunosorbent assays (ELISAs) and other immunoassays. Gelatin is also a component in

       various gels used for biochemical and electrophoretic analysis, including enzymography gels.


## EXAMPLES

30     The following examples are provided solely to illustrate the claimed invention. The present

       invention, however, is not limited in scope by the exemplified embodiments, which are intended

       as illustrations of single aspects of the invention only, and methods which are functionally

       .equivalent are within the scope of the invention. Indeed, various modifications of the invention in

       addition to those described herein will become apparent to those skilled in the art from the

35     foregoing description and accompanying drawings. Such modifications are intended to fall within

       the scope of the appended claims.

5    Example 1:  Sequencing of Bovine Procollagen Type I α1

Experiments were performed to generate α1(I) collagen gene fragments by PCR from a commercial
bovine aorta smooth muscle cDNA library (Stratagene #936705) that had been a successful source of
bovine collagen (I) alpha 2 gene fragments in initial PCR experiments. In this initial screening process,
PCR primers were designed from the bovine mRNA sequence (Shirai et al. (1998) Matrix Biology 17:85-
10   88) of collagen (I) α2, and PCR amplifications performed, and DNA fragments were obtained. Although
the commercial library was shown to contain the complete coding region of the bovine collagen (I) alpha
2 gene, attempts to generate fragments of the bovine α1(I) collagen gene using a variety of human α1(I)
collagen sequence PCR primers proved unsuccessful. An alternative source of a cDNA pool likely to
contain a bovine α1(I) collagen transcript was sought.

15

An ATCC bovine skin cell line (CRL-6054; skin, normal, bovine) was grown to approximately 60%
confluency and total RNA was isolated (Qiagen RNeasy). A cDNA pool was prepared from the resulting
RNA by RT-PCR (Clontech RT-for-PCR reagents). This cDNA pool was used as the template source for
subsequent PCR experiments of overlapping gene fragments.

20

Primers were designed from known human α1(I) collagen mRNA sequence, and used to amplify
overlapping segments of the open reading frame (ORF) of the gene. (Mackay et al. (1993) Human
Molecular Genetics 2(8):1155-1160). The PCR primers were engineered to amplify fragments located in
the triple helical coding region of the human α1(I) collagen gene and are set forth in Table 1.

25

Table 1

| SEQ ID NO: | PRIMER | SEQUENCE |
|---|---|---|
| 13 | SSCP 1F | CCGGCTCCTGCTCCTCTTAG |
| 14 | SSCP 1REV | GCCAGGAGCACCAGCAATAC |
| 15 | SSCP 2F | GCTGATGGACAGCCTGGTGC |
| 16 | SSCP 2REV | GCCCTGGAAGACCAGCTGCA |
| 17 | SSCP 3F | CCTGGCCTTAAGGGAATGCC |
| 18 | SSCP 3REV | GCGCCAGGAGAACCGTCTCG |
| 19 | SSCP 4F | CCGAAGGTTCCCCTGGACGA |
| 20 | SSCP 4REV | CGGTCATGCTCTCGCCGAAC |

The primers were used to obtain four overlapping bovine PCR fragments covering the triple helical
portion of the bovine α1(I) collagen gene. PCR (Clontech, Advantage GC-Rich cDNA PCR kit; all PCR

5    primers used @ 100 pmol each per reaction) was performed using a thermal cycler (Hybaid, non-
refrigerated) under the following conditions:

        Step 1:      94°C for 4 minutes

        Step 2:      28 cycles of :

                    68°C  for 3 minutes

10                        94°C  for 30 seconds

                    60°C  for 30 seconds

        Step 3:      68°C  for 10 minutes

                    30°C  for 1 second

                    Hold @ room temperature

15

All PCR products were initially screened by gel electrophoresis, and those of the predicted size were
purified by agarose gel electrophoresis and/or column purification (Qiagen Qiaquick).   To facilitate
sequencing, the selected PCR fragments were cloned into a vector (pCRII-TOPO kit, Invitrogen).
Multiple clones of each PCR fragment were sequenced with an external vector sequencing primers (M13

20    forward and reverse) using an ABI 373 automated sequencer (ABI PRISM® BigDye™ Terminator Cycle
Sequencing Kit, Perkin-Elmer).  Sequence data obtained was analyzed with the use of SEQMAN software
(DNASTAR) and a consensus sequence determined for the cloned fragments.

The resulting bovine α1(I) collagen sequence obtained was used to design internal bovine collagen
25    sequencing primers, which were then used to complete the sequencing of these bovine clones. These
primers were designed with the aid of primer design software (RightPrimer, BioDisk), and are set forth in
Table 2.

Table 2

| SEQ ID NO: | PRIMER | SEQUENCE |
|---|---|---|
| 21 | B C1A1 SP 502F | CCCCAGTTGTCTTACGGCTATG |
| 22 | B C1A1 SP 502REV | CATAGCCGTAAGACAACTGGGG |
| 23 | B C1A1 SP 886F | GGTAGCCCCGGTGAAAATG |
| 24 | B C1A1 SP 886REV | CATTTTCACCGGGGCTACC |
| 25 | B C1A1 SP 1302F | GCCCCAAGGGTAACAGCGGT |
| 26 | B C1A1 SP 1302REV | ACCGCTGTTACCCTTGGGGC |
| 27 | B C1A1 SP 1560F | TCCTGGCCCTGCTGGCCCCAAA |
| 28 | B C1A1 SP 1560REV | TTTGGGGCCAGCAGGGCCAGGA |
| 29 | B C1A1 SP 1770F | TGGACCTAAAGGTGCTGCTGGA |

| 30 | B ClAl SP 1770REV | TCCAGCAGCACCTTTAGGTCCA |
| 31 | B ClAl SP 1997F | GAACAGGGTGTTCCTGGAGA |
| 32 | B ClAl SP 1997REV | TCTCCAGGAACACCCTGTTC |
| 33 | B ClAl SP 2289F | GGCAAAGATGGCGTCCGT |
| 34 | B ClAl SP 2289REV | ACGGACGCCATCTTTGCC |
| 35 | B ClAl SP 2592F | GCTAAAGGCGAACCTGGCGA |
| 36 | B ClAl SP 2592REV | TCGCCAGGTTCGCCTTTAGC |
| 37 | B ClAl SP 3198F | GCCGGCAAGAGCGGTGATCGT |
| 38 | B ClAl SP 3198REV | ACGATCACCGCTCTTGCCGGC |
| 39 | B ClAl SP 3648F | CGATGGTGGCCGCTACTAC |
| 40 | B ClAl SP 3648REV | GTAGTAGCGGCCACCATCG |
| 41 | B ClAl SP 4007F | AGAGCATGACCGAAGGGCGAATT |
| 42 | B ClAl SP 4007REV | AATTCGCCCTTCGGTCATGCTCT |

After producing bovine PCR products with the eight SSCP human primers shown in Table 1 (SEQ ID NOs:13 through 20), three additional PCR fragments were amplified, overlapping the initial bovine clones, and extending to the putative ends (by analogy with the human α1(I) collagen sequence) of the ORF. The PCR primers used for this amplification are set forth in Table 3.

Table 3

| SEQ ID NO: | PRIMER | SEQUENCE |
| --- | --- | --- |
| 43 | H AVR II F | TTAATTCCTAGGATGTTCAGCTTTGTGGACCTCCGGCTC |
| 44 | H EAR 1 F | TGCCACTCTGACTGGAAGAGTGGAGAGTACTG |
| 45 | H NOT1 REV | TTTTCCTTTTGCGGCCGCTTACAGGAAGCAGACAGGGCCAACGTC |

The resulting DNA fragments were cloned and sequenced, and a consensus sequence was established for most of the ORF of the gene by pairing of the following primers: H AVR II (SEQ ID NO:43) with SSCP 1REV (SEQ ID NO:14); H EAR 1 F (SEQ ID NO:44) with H NOT1 REV (SEQ ID NO:45); and SSCP 4F (SEQ ID NO:19) with H NOT1 REV (SEQ ID NO:45).

To obtain the 5' and 3' ends of the cDNA clone, nested PCR primers were designed from the bovine sequence by RACE (rapid amplification of cDNA ends) methodology (SMART RACE cDNA Amplification Kit, Clontech), and with the aid of primer design software. For increased specificity, the primers were designed to have particularly high melting temperatures. The designed primers are set forth in Table 4.

5

Table 4

| SEQ ID NO: | PRIMER | SEQUENCE |
|---|---|---|
| 46 | GS BC1A1 118REV | GTCATGGTACCTGAGGCCGTTCTGTACGCA |
| 47 | GS BC1A1 190REV | ACGTCATCGCACAGCACGTTGCCGTTGTC |
| 48 | GS BC1A1 213REV | AGGACAGTCCTTAAGTTCGTCGCAGATCACGTCA |
| 49 | GS BC1A1 761REV | AGGGAGGCCAGCTGTTCCAGGCAATC |
| 50 | GS BC1A1 3085F | CCGAAGGTTCCCCTGGACGAGATGGTT |
| 51 | GS BC1A1 3305F | CGTGGTGACAAGGGTGAGACAGGCGAACA |
| 52 | GS BC1A1 3675F | CGGGCTGATGATGCCAATGTGGTCCGT |
| 53 | GS BC1A1 3905F | AACATGGAAACCGGTGAGACCTGTGTATACCC |

The total bovine mRNA described above was further utilized to prepare new cDNA pools with the
necessary external priming sites for use as PCR templates. PCR products were obtained at both the 5'
and 3' ends of the gene using: (1) touchdown PCR techniques; (2) the newly designed bovine RACE

10     PCR primers; and (3) materials supplied in the kit. Two touchdown PCR programs were used in a
Peltier-cooled thermal cycler using the following protocol and conditions:

72 °C – 68 °C touchdown program I:
Step 1: 8 cycles with the following conditions :

15               94 °C   for 10 seconds
              72 °C   for 10 seconds, each cycle thereafter drop 0.5°C
              72 °C   for 3 minutes

Step 2: 28 cycles of the following conditions:

20               94 °C for 10 seconds
              68 °C for 10 seconds
              72 °C for 3 minutes
              72 °C for 10 minutes
              4 °C HOLD

25

68 °C – 64 °C touchdown program II:
Step 1: 8 cycles of the following conditions:
              94 °C for 10 seconds
              68 °C for 10 seconds, each cycle thereafter drop 0.5°C

30               72 °C for 3 minutes
Step 2: 28 cycles of the following conditions:

5          94 °C for 10 seconds
           64 °C for 10 seconds
           72 °C for 3 minutes
           72 °C for 10 minutes
           4 °C HOLD

10
The resulting fragments were examined by 1.2% agarose gel electrophoresis, and subsequent cloning and sequencing analysis was performed. PCR products resulting from both programs were used. The resulting sequences overlapped the previously cloned bovine α1(I) collagen sequences, and encoded the 5' and 3' ends of the ORF as well as the contiguous untranslated cDNA regions. The nucleotide sequence

15   for bovine procollagen type I α1 is shown in Figures 1A through 1C (SEQ ID NO:1). The corresponding amino acid sequence is described in Figures 2A through 2D (SEQ ID NO:2).

As shown in Figures 13A through 13I, translated bovine collagen ORF sequences were aligned with known human (HU), mouse (MUS), dog (CANIS), bullfrog (RANA), and Japanese newt (CYNPS)

20   sequences. The translated bovine sequence also aligns with published amino acid sequence fragments of the triple helical repeat domains of bovine α1(I) collagen. (See, e.g., Miller (1984) Extracellular Matrix Biochemistry, ed. Piez, et al., Elsevier Science Publishing, New York, pp. 41-81; and SWISSPROT database accession number p02453.) Numerous differences between the predicted bovine α1(I) collagen protein sequence provided by the present invention and previously known bovine protein sequences were

25   noted. Some of these differences include substitutions of amino acids that are typically difficult to distinguish by protein sequencing (i.e., glutamine/glutamic acid and aspartic acid/asparagine). The polynucleotide sequence disclosed herein as SEQ ID NO:1 suggests these known bovine α1(I) collagen protein sequences may include errors, and therefore may, for example, be precluded for use in construction of a synthetic gene encoding authentic bovine α1(I) collagen gene by amino acid back-

30   translation.

Example 2: Sequencing of Bovine Procollagen Type III α1

Bovine procollagen type III α1 cDNA was isolated as follows. Using 1μl of Bovine Liver Poly A⁺ RNA (Clontech, Cat No. 6810-1), a cDNA strand was constructed with a reverse transcription

35   reaction set up as follows using the Ambion Retroscript kit (Cat No. 1710):

          1 μl     RNA (1μg)
          4 μl     dNTPs mix (2.5 mM each)

60

|        |                                    |
|--------|------------------------------------|
| 2 µl   | Oligo dT first strand primers      |
| 9 µl   | Sterile water                      |

5

This solution was incubated at 75°C for 3 min and then placed on ice. The following was then added:

|        |                              |
|--------|------------------------------|
| 2 µl   | 10 X Alternative RT-PCR buffer |
| 1 µl   | Placental RNAase inhibitor   |
| 1 µl   | M-MLV reverse transcriptase  |

10   The reaction was allowed to proceed at 42°C for 90 min and inactivated by incubation at 92°C for 10 min. The reaction was then stored at –20°C.

Oligonucleotide primers were designed based on the sequence from the human procollagen type 3 α1 cDNA (Genbank Accession No. X14420) and the bovine procollagen type 3 α1 cDNA

15   (Genbank Accession No. L47641). PCR was performed using the first strand cDNA prepared above and the primers as set forth in Table 5.

Table 5

| SEQ ID NO: | PRIMER | SEQUENCE |
|------------|--------|----------|
| 54 | CIII-1 | GACATGATGAGCTTTGTGCAAAAGG |
| 55 | CIII-6 | TTTGGTTTATAAAAAGCAAACAGGGCC |
| 56 | A3-N | TCTCATGTCTGATATTTAGACATG |
| 57 | CIII-4 | GGACTAATGAGGCTTTCTATTTGTCC |
| 58 | CIII-2 | GGCACCATTCTTACCAGGCTCACC |
| 59 | CIII-3 | TGGGTCCCGCTGGCATTCCTGG |
| 60 | CIII-5 | CCAGGACAACCAGGCCCTCCTGG |

20   The PCR reaction conditions were as follows:

|         |                                                        |
|---------|--------------------------------------------------------|
| 5 µl    | Reverse transcriptase reaction above                   |
| 5 µl    | 10 X Reaction Buffer                                   |
| 1.5 µl  | dNTPs mix (2.5mM each)                                  |
| 1.5 µl  | Primer CIII-1 (5µM)                                    |
| 1.5 µl  | Primer CIII-6 (5µM)                                    |
| 0.5 µl  | Platinum pfx polymerase (Life Tech., Cat No. 11708-013) |
| 35 µl   | Sterile Water                                          |

50 µl    Total Volume

The reaction mixture was cycled in a Techne Genius DNA Thermal Cycler as follows:

|       |         |              |
|-------|---------|--------------|
| 80°C  | 2 min   |              |
| 94°C  | 2 min   | for 1 cycle  |
| 94°C  | 30 sec  |              |
| 55°C  | 30 sec  | for 35 cycles |
| 68°C  | 4.5 min |              |
| 68°C  | 5 min   | for 1 cycle  |

A DNA band of approximately 4500 bp was identified in the reaction using primers CIII-1 (SEQ ID NO:54) and CIII-6 (SEQ ID NO:55). This DNA fragment was purified using a Qiagen QiaQuick Gel Extraction Kit (Cat No. 28704), and ligated to plasmid vector pCR ®-Blunt (Invitrogen Zero Blunt ™ PCR Cloning Kit, Cat NO. K2700-20). The resultant recombinant plasmids were introduced into competent *E. coli* (JM109) and stocks of recombinant plasmid DNA generated using the Qiagen Qiaprep Spin Miniprep Kit (Cat No. 27106). DNA was sequenced on an LI-COR 4200 Automated Fluorescent Sequencer (MWG-Biotech UK Ltd.).

In areas where high quality sequence was available from partial bovine sequence as described in Genbank Accession Nos. L47641 and PO4258 (amino acid only), the sequences of the bovine α1(III) cDNA of the present invention were shown to be identical. In other areas, sequence highly homologous to the human procollagen α1(III) cDNA (Genbank Accession No. X14420) and porcine procollagen α1(III) cDNA (Genbank Accession Nos. C94995, C94535, and C94565) was identified.

Since the 5' primer CIII-1 (SEQ ID NO:54) was designed using to the human sequence and was thus integrated into the newly isolated cDNA, the native bovine sequence was identified in this area as follows. An additional PCR fragment of approximately 3700 bp was amplified from bovine cDNA using primers A3-N (SEQ ID NO:56) and CIII-4 (SEQ ID NO:57). Primer A3-N was designed according to the sequence of the human procollagen type 3 α1 cDNA, in the region immediately upstream of the start codon. The resulting fragment was sequenced and confirmed using primers CIII-1 (SEQ ID NO: 54) and CIII-6 (SEQ ID NO: 55).

62

5       In summary, full length cDNA for bovine procollagen α1(III) was isolated by RT-PCR from
         bovine mRNA. Following extensive sequencing (three independent PCR reactions) using primers
         described in Table 5 and sequencing primers designed using methods described in Example 1 and
         methods known to those of skill in the art, 4428 bp of contiguous sequence containing the start
         codon ATG and stop codon TAA was assembled (Figures 3A through 3C, SEQ ID NO:3). The
10      deduced amino acid sequence is shown in Figures 4A through 4D (SEQ ID NO:4). Two cDNA
         sequence variants of bovine α1(III) collagen (SEQ ID NO:3 and SEQ ID NO:5) were obtained
         and confirmed by sequencing of multiple clones. SEQ ID NO:3 and the corresponding amino
         acid sequence (SEQ ID NO:4) correspond to the appropriate region within the sequence of
         Genbank Accession No. L47641. Comparatively, SEQ ID NO:5 (Figures 5A through 5C)
15      displayed a C to T base substitution, leading to the codon change AAC to AAT (both encoding
         Asp); an A to G base substitution, leading to the codon change AAT to GAT (Asp to Asn
         substitution as residue 1232); and a T to C base subtitution, leading to the codon change GTC to
         GCC (Val to Ala substitution at residue 1382). The corresponding deduced amino acid sequence
         is shown in Figures 6A through 6D (SEQ ID NO:6). The above sequences were identical to
20      available partial bovine sequences (Genbank Accession Nos. L47641 and PO4258).


         Example 3: Sequencing of Porcine Procollagen Type 1 α1
         Porcine procollagen type I α1 cDNA was isolated using the following methods. Frozen porcine
         liver (obtained from Anglo Dutch Meats, Charing, Kent) was placed in liquid nitrogen and
25      pulverized with a pestle and mortar. Approximately 800 mg of the crushed material was added to
         5ml lysis binding solution as described in the Ambion RNAqeous Kit (Cat No. 1912). Following
         Dounce homogenization, any debris was removed by centrifugation (12,000 x g, 2 min) and an
         additional 5ml lysis binding solution was added to the homogenate. Ten milliliters of 64%
         ethanol was added, mixed, and the lysate/ethanol mixture was applied to the RNAqeous filter
30      (Ambion). Each filter was loaded with 2 x 700µl lysate/ethanol mixture and centrifuged (12,000
         x g, 1 min). The filters were then washed once with 700 µl Wash Solution No. 1 (Ambion) and
         twice with 500µl Wash Solution No. 2/3 (Ambion), and centrifuged after each wash step with a
         final centrifugation step after the final wash (12,000 x g, 15 sec). The RNA was eluted from the
         filter by applying 2 x 60µl preheated (95°C) Elution solution (Ambion) to the center of the filter
35      and centrifugation (12,000 x g, room temp, 30 sec). The four eluates of four purifications of RNA
         (total concentration ~ 15µg) were pooled and precipitated with 0.5 x vol lithium chloride
         (Ambion) overnight at –20°C. This was then centrifuged at 12,000 x g, 15 min, 4 C, and the

5   pellet washed with 70% ethanol. The pellet was then air dried and resuspended in 15μl sterile

water and stored at −70°C.

Using 1μl of the RNA isolated above, a cDNA strand was constructed, using the reverse

transcription reaction performed as described above in Example 2. Oligonucleotide primers based

10  on the sequence from the human procollagen α1(I) cDNA (Genbank Accession No. NM000088)

and the porcine procollagen α1(I) cDNA (Genbank Accession No. C94935) were designed. PCR

was then performed, using methods described in Example 2, with the first strand cDNA prepared

and primers corresponding to known human or porcine DNA (Table 6).

15                                     Table 6

| SEQ ID NO | PRIMER | SEQUENCE |
|---|---|---|
| 61 | HU1-5 | GACATGTTCAGCTTTGTGGACCTC |
| 62 | PCA1-6 | AGTTTACAGGAAGCAGACAG |
| 63 | A1-N | CTACATGTCTAGGGTCTAGACATG |
| 64 | PCA1-4 | AGGCGCCAGGCTCGCCAGGCTCAC |
| 65 | PCA1-3 | AGTTGTCTTATGGCTATGATGAG |

The reverse transcriptase-PCR was carried out on RNA purified from porcine liver and a DNA

band of approximately 4500 bp was identified in the reaction, using primers HU1-5 (SEQ ID

NO:61) and PCA1-6 (SEQ ID NO:62). This DNA fragment was purified, cloned, and sequenced

20  as described in Example 2.

Since the 5' primer HU1-5 (SEQ ID NO:61) was designed according to the human sequence and

thus was integrated into the newly isolated cDNA described above, the native porcine sequence

needed to be confirmed in this area. An additional PCR fragment of approximately 750 bp was

25  consequently amplified from porcine cDNA using primers A1-N (SEQ ID NO:63) and PCA1-4

(SEQ ID NO:64). Primer A1-N (SEQ ID NO:63) was designed according to the sequence of the

human procollagen α1(I) cDNA in the region immediately upstream of the start codon. This

fragment was sequenced to confirm that the full-length porcine α1(I) cDNA fragment generated

using primers HU1-5 (SEQ ID NO:61) and PCA1-6 (SEQ ID NO:62) had the authentic porcine 5'

30  end rather than a hybrid sequence introduced by the human sequence based primer.

In summary, full-length cDNA for porcine procollagen α1(I) was isolated by RT-PCR from

porcine liver. Following extensive sequencing (three independent PCR reactions), 4425 bp of

contiguous sequence containing the start codon ATG and stop codon TAA was assembled as

64

5    shown in Figures 7A through 7C (SEQ ID NO:7). This sequence was identical to the available
     partial porcine sequence (Genbank Accession Nos. C94935 and AU058670). The sequence
     shows a high degree of homology to the human procollagen type 1 α1 sequence (Accession No.
     G4502944). The corresponding amino acid sequence of the porcine type 1 α1 collagen is shown
     in Figures 8A through 8D (SEQ ID NO:8).

10

     Example 4: Sequencing of Porcine Procollagen Type I α2
     Porcine procollagen type I α2 cDNA was isolated using the following methods. Total RNA
     isolation, reverse transcription, and PCR were performed essentially as described above in
     Example 2. Oligonucleotide primers were designed based on the sequence from the human α2(I)

15   procollagen (Genbank Accession No. NM000089) and the porcine α2(I) procollagen (Genbank
     Accession No. AU058497). Primers used are set forth in Table 7.

Table 7

| SEQ ID NO | PRIMER | SEQUENCE |
| --- | --- | --- |
| 66 | HU2-5 | GACATGCTCAGCTTTGTGGATACG |
| 67 | PCA2-6 | AGCTGGACCAGGCTCACCAACAA |
| 68 | PCA2-5 | TGGTGCTAAGGGTGCTGCTGGCCT |
| 69 | PCA2-8 | AGGTTCACCCACTGATCCAGCAACA |
| 70 | PCA2-7 | TCCCTCTGGAGAGCCTGGTACTGCT |
| 71 | PCA2-2 | TGGAAGTTTGGGTTTTAAACTTCCC |
| 72 | A2-N | ACACAAGGAGTCTGCATGTCT |

20   The following primer pairs were used to generate three overlapping fragments of the following
     sizes: 1054 bp DNA, using primer HU2-5 (SEQ ID NO:66) and primer PCA2-6 (SEQ ID
     NO:67); 1766 bp DNA, using primer PCA2-5 (SEQ ID NO:68) and primer PCA2-8 (SEQ ID
     NO:69); and 1937 bp DNA, using primer PCA2-7 (SEQ ID NO:70) and primer PCA2-2 (SEQ ID
     NO:71). These DNA fragments were isolated, subcloned and sequenced using methods described

25   above. Sequence highly homologous to the full-length human collagen α2(I) gene (Genbank
     Accession No. NM000089) or to the partial porcine α2(I) sequence (Genbank Accession No,
     AU058497) was identified.

     As the 5' primer HU2-5 (SEQ ID NO:66) used in the cloning of the porcine procollagen type 1 α2

30   cDNA was designed using to the human sequence and was thus integrated into the newly isolated
     cDNA, a further PCR fragment of approximately 1100 bp was consequently amplified from
     porcine cDNA using primers A2-N (SEQ ID NO:72) and PCA2-6 (SEQ ID NO:67). Primer A2-
     N had been designed according to the sequence of the human (Genbank Accession

5      No. NM0000890) and bovine (Genbank Accession No. AB008683) procollagen α2(I) cDNA in
       the region immediately upstream of the start codon. The sequence of this DNA fragment
       confirmed that the full-length fragment generated using primers HU2-5 and PCA2-2 had the
       authentic porcine 5' end. The full-length nucleotide sequence for the porcine α2(I) collagen gene
       is shown in Figures 9A through 9C (SEQ ID NO:9). The corresponding amino acid sequence is
10     described in Figures 10A through 10C (SEQ ID NO:10).


       Example 5:  Sequencing of Porcine Procollagen Type III α1
       Porcine procollagen type III α1 cDNA was isolated using the following methods. Total RNA was
       isolated from frozen porcine liver, reverse transcription, and PCR was performed as described
15     above in Example 2. Oligonucleotide primers were designed based on the sequence from the
       human procollagen type 3 α1 cDNA (Genbank Accession No. X14420) and the porcine
       procollagen type 3 α1 cDNA (Genbank Accession Nos. C94995, C94535, and C94565). These
       primers are set forth in Table 5 above.


20     RT-PCR was carried out on RNA purified from porcine liver and a DNA band of approximately
       4500 bp was identified in the reaction using primers CIII-1 (SEQ ID NO:54) and CIII-6 (SEQ ID
       NO:55). This DNA fragment was purified, subcloned, and sequenced as described above. In
       areas where high quality sequence was available from partial porcine sequence as described in
       Genbank Accession Nos. C94565, C94535, and C95995, the sequence of the new cDNA was
25     shown to be identical. In other areas sequence highly homologous to the human procollagen
       α1(III) cDNA (Genbank Accession No. X14420) and bovine procollagen α1(III) cDNA
       (sequences derived from the current inventions and Genbank Accession No. L47641) were
       identified.


30     As the 5' primer CIII-1 was designed using the human sequence and was integrated into the
       newly isolated cDNA, the native porcine sequence needed to be confirmed. A further PCR
       fragment of approximately 3700 bp was consequently amplified from porcine cDNA using
       primers A3-N (SEQ ID NO:56) and CIII-4 (SEQ ID NO:57). Primer A3-N was designed
       according to the sequence of the human procollagen α1(III) cDNA in the region immediately
35     upstream of the start codon. This fragment was sequenced to confirm that the full-length
       fragment generated using primers CIII-1 and CIII-6 had the authentic porcine 5' sequence.

5      In summary, a full-length cDNA for porcine α1(III) procollagen was isolated by RT-PCR from
       porcine liver. Following extensive sequencing (three independent PCR reactions) 4428 bp of
       contiguous sequence containing the start codon ATG and stop codon TAA was assembled.
       (Figures 11A through 11C, SEQ ID NO:11.). This sequence was identical to available partial
       porcine sequence (Genbank Accession Nos. C94565, C94535, and C95995). Overall the
10     sequence showed a high degree of homology to the human α1(III) procollagen cDNA (Genbank
       Accession No. X14420) and bovine α1(III) procollagen cDNA (from the current invention and
       Genbank Accession Nos. L47641 and PO4258). The deduced amino acid sequence for porcine
       type III α1 collagen is presented in Figures 12A through 12C (SEQ ID NO:12).


15     Example 6: Production of Animal Collagens and Gelatins in Transgenic Plants

       The cDNAs encoding an animal collagen of the present invention, an α subunit of prolyl 4-
       hydroxylase, and a β subunit of prolyl 4-hydroxylase are cloned into an appropriate plant
       expression vector that contains the necessary elements to properly express a foreign protein. Such
       elements may include, for example a signal peptide, promoter and a terminator. (See, e.g., Rogers
20     et al., supra; Schardl et al., supra; Berger et al., supra.) For example, pVL vectors have been
       described in the art. (See, e.g., A. Lamberg et al. (1996) J. Biol. Chem.271:11988-11995.) These
       recombinant pVL vectors are used as a gene source for the construction of plant expression
       vectors using conventional methods known in the art. In order to express the collagen in plant or
       plant cells, the nucleic acid sequences are operably linked, for example, to a CaMV 35S promoter.
25     The nucleic acid sequences encoding an α subunit or βsubunit of prolyl 4-hydroxylase are
       operably linked to a CaMV 35S promoter, and may be present on the same plasmid or on different
       plasmids to produce a biologically active prolyl 4-hydroxylase.

       The expression vectors are transformed into plants or plant cells using transformation techniques
30     well known in the art. The expression clones are selected by, for example, northern and western
       blotting, and can be cultivated in a fermentor to generate a cell mass for purification of
       recombinant collagen.

       The expression of the α subunit and the β subunit of prolyl 4-hydroxylase and animal collagen is
35     screened, for example, by immunoblotting using three hundred (300) mg cell pellets extraction in
       10mM Tris, pH 7.8, 100mM NaCl, 100mM Glycine, 10uM DTT, 0.1% Triton X100, 2uM
       Leupeptin, and 0.25mM PMSF. The proteins in the extract are separated with 4-20% SDS-

5    PAGE, and transferred to a nitrocellulose membrane to be probed with antibodies against the α subunit and β subunit of prolyl 4-hydroxylase and the animal collagen.

To characterize recombinant animal collagen produced in plants or plant cells, the following protocol is carried out:

10

1.   Suspend and homogenize cell pellets in 1M NaCl, 0.05M Tris, pH7.4 and stir for 1 hour at 4°C. Collect the supernatant by centrifugation at 4°C;

2.   Add 7.5ml acetic acid to the supernatant and incubate at 4°C for 2 hours. Collect the pellet by centrifugation at 4°C;

15   3.   Wash the pellet twice with 2M NaCl, 0.05M Tris, pH 7.4;

4.   Re-dissolve in 2M Urea, 0.2M NaCl, 0.05M Tris, pH 7.4;

5.   Dialyze against 2M Urea, 0.2M NaCl, 0.05M Tris, pH 7.4;

6.   Run through a DEAE-cellulose column. Collect the flow-through;

7.   Add acetic acid to 0.5M and add NaCl to 0.9M and incubate for 2 hours at 4°C;

20   8.   Collect pellets by centrifugation;

9.   Resuspend the pellet in 0.5M acetic acid and stir overnight at 4°C;

10.  Digest the pellet with 0.1mg/ml pepsin for 2 hours;

11.  Add saturated Tris buffer and adjust pH to 7.4;

12.  Incubate overnight to inactivate pepsin;

25   13.  Add NaCl to 0.9M and acetic acid to 0.5M, Incubate for 2 hours at 4°C;

14.  Collect the pellet by centrifugation at 4°C;

15.  Wash the pellet with 2M NaCl, 0.05M Tris, pH 7.4;

16.  Dissolve in 2M Urea, 150M NaCl and 0.05M Tris, pH 7.4; and

17.  Heat the sample at 56°C for 5 min and then load to Bio-Gel TSK 40 column operated by

30       HPLC system.

The resulting purified collagen is characterized by amino acid composition analysis.

Various modifications and variations of the described methods and systems of the invention will

35   be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention

5    which are obvious to those skilled in molecular biology or related fields are intended to be within
     the scope of the following claims.  All references cited herein are incorporated by reference herein
     in their entirety.

5                                          . CLAIMS

What is claimed is:

1.    An isolated and purified polypeptide comprising a bovine or porcine polypeptide selected
10        from the group consisting of:

      (i)     α1(I) collagens, α2(I) collagens, and α1(III) collagens; and

      (ii)    fragments and variants of (i).
15
2.    An isolated and purified polypeptide comprising a bovine α1(I) collagen or fragments or
      variants thereof.

3.    The polypeptide of claim 2, wherein the polypeptide is single-chain.
20
4.    The polypeptide of claim 2, wherein the polypeptide is homotrimeric.

5.    The polypeptide of claim 2, wherein the polypeptide is heterotrimeric.    .  ·

25    6.    The polypeptide of claim 2, wherein the polypeptide comprises the amino acid sequence
      of SEQ ID NO:2 or fragments or variants thereof.

7.    A composition comprising the polypeptide of claim 2.

30    8.    An isolated and purified polynucleotide encoding a bovine α1(I) collagen or fragments or
      variants thereof.

9.    An isolated and purified polynucleotide complementary to the polynucleotide of claim 8.

35    10.   An isolated and purified polynucleotide encoding SEQ ID NO: 2 or fragments or variants
      thereof.

11.   A composition comprising the polynucleotide of claim 8.

70

5   12.     An expression vector comprising the polynucleotide of claim 8.

    13.     A host cell comprising the polynucleotide of claim 8.

    14.     The host cell of claim 13, wherein the host cell is a prokaryotic host cell.
10
    15.     The host cell of claim 13, wherein the host cell is a eukaryotic host cell.

    16.     The host cell of claim 13, wherein the host cell is selected from the group consisting of an
            animal cell, a yeast cell, a plant cell, an insect cell, and a fungal cell.
15
    17.     A transgenic animal comprising the polynucleotide of claim 8.

    18.     A transgenic plant comprising the polynucleotide of claim 8.

20  19.     A method for producing a bovine α1(I) collagen, the method comprising:

            (a)     culturing the host cell of claim 13 under conditions suitable for expression of the
                    polypeptide; and

25          (b)     recovering the polypeptide from the host cell culture.

    20.     A recombinant collagen comprising the amino acid sequence of SEQ ID NO:2 or
            fragments or variants thereof.

30  21.     A recombinant gelatin comprising the amino acid sequence of SEQ ID NO:2 or fragments
            or variants thereof.

    22.     An isolated and purified polypeptide comprising a bovine α1(III) collagen or fragments
            or variants thereof.
35
    23.     An isolated and purified polypeptide comprising a porcine α1(I) collagen or fragments or
            variants thereof.

5   24.   An isolated and purified polypeptide comprising a porcine α2(I) collagen or fragments or variants thereof.

    25.   An isolated and purified polypeptide comprising a porcine α1(III) collagen or fragments or variants thereof.

10

    26.   A method for synthesizing an animal collagen, the method comprising:

          (a)    introducing into a host cell at least one expression vector comprising a polynucleotide sequence encoding an animal collagen or procollagen, and at least

15                 one expression vector comprising a polynucleotide sequence encoding a post-translational enzyme, under conditions which permit the expression of the polynucleotides; and

          (b)    isolating the animal collagen.

20

    27.   The method of claim 26, wherein the post-translational enzyme is selected from the group consisting of prolyl hydroxylase, peptidyl prolyl isomerase, collagen galactosyl hydroxylysyl glucosyl transferase, hydroxylysyl galactosyl transferase, C-proteinase, N-proteinase, lysyl hydroxylase, and lysyl oxidase.

25

    28.   The method of claim 26, wherein the post-translational enzyme is selected from the same species as the animal collagen.

    29.   The method of claim 26, wherein the host cell is selected from the same species as the

30          animal collagen.

    30.   The method of claim 26, wherein the cell does not endogenously produce collagen.

    31.   The method of claim 26, wherein the cell does not endogenously produce a post-

35          translational enzyme.

    32.   A host cell comprising at least one expression vector encoding an animal and at least one expression vector encoding a post-translational enzyme

5     33.    A recombinant animal collagen f one type substantially free of any other type.

        34.    The recombinant animal collagen of claim 33, wherein the collagen of one type is selected from the group consisting of type I, type II, type III, type IV, type V, type VI, type VII, type VIII, type IX, type X, type XI, type XII, type XIII, type XIV, type XV,

10        type XVI, type XVII, type XVIII, type XIX, and type XX collagen.

        35.    A method for producing recombinant animal gelatin, the method comprising:

                (a) providing recombinant animal collagen; and

15

                (b) deriving recombinant animal gelatin therefrom.

        36.    A method for producing recombinant animal gelatin, the method comprising producing recombinant animal gelatin directly from an altered animal collagen construct.

20

CAGACGGGAGTTTCTCCTCGGGGTCGGAGCAGGAGGCACGCGGAGTGTGAGGCCA
CGCATGAGCGGACGCTAACCCCCACCCCAGCCGCAAAGAGTCTACATGTCTAGGG
TCTAGACATGTTCAGCTTTGTGGACCTCCGGCTCCTGCTCCTCTTAGCGGCCACC
GCCCTCCTGACGCACGGCCAAGAGGAGGGCCAGGAAGAAGGCCAAGAAGAAGACA
TCCCACCAGTCACCTGCGTACAGAACGGCCTCAGGTACCATGACCGAGACGTGTG
GAAACCCGTGCCCTGCCAGATCTGTGTCTGCGACAACGGCAACGTGCTGTGCGAT
GACGTGATCTGCGACGAACTTAAGGACTGTCCTAACGCCAAAGTCCCCACGGACG
AATGCTGCCCCGTCTGCCCCGAAGGCCAGGAATCACCCACGGACCAAGAAACCAC
CGGAGTCGAGGGACCGAAAGGAGACACTGGCCCCCGAGGCCCAAGGGGACCCGCC
GGCCCCCCCGGCCGAGATGGCATCCCTGGACAACCTGGACTTCCCGGACCCCCTG
GACCCCCCGGACCTCCCGGACCCCCTGGCCTCGGAGGAAACTTTGCTCCCCAGTT
GTCTTACGGCTATGATGAGAAATCAACAGGAATTTCCGTGCCTGGTCCCATGGGT
CCTTCTGGTCCTCGTGGTCTCCCTGGCCCCCCTGGCGCACCTGGTCCCCAAGGTT
TCCAAGGCCCCCCTGGTGAGCCTGGCGAGCCAGGAGCCTCAGGTCCCATGGGTCC
CCGTGGTCCCCCTGGCCCCCCTGGCAAGAACGGAGATGATGGCGAAGCTGGAAAG
CCTGGTCGTCCTGGTGAGCGCGGGCCTCCCGGACCTCAGGGTGCTCGGGGATTGC
CTGGAACAGCTGGCCTCCCTGGAATGAAGGGACACAGAGGTTTCAGTGGTTTGGA
TGGTGCCAAGGGAGATGCTGGTCCTGCTGGCCCCAAGGGCGAGCCTGGTAGCCCC
GGTGAAAATGGAGCTCCTGGTCAGATGGGCCCCCGTGGTCTGCCTGGTGAGAGAG
GTCGCCCTGGAGCCCCTGGCCCTGCTGGTGCTCGAGGAAATGATGGTGCGACTGG
TGCTGCTGGGCCCCCTGGTCCCACTGGCCCCGCTGGTCCTCCTGGTTTCCCTGGT
GCTGTGGGTGCTAAGGGTGAAGGTGGTCCCCAAGGACCCCGAGGTTCTGAAGGTC
CCCAGGGTGTACGTGGTGAGCCTGGCCCCCCTGGCCCTGCTGGTGCTGCTGGCCC
TGCTGGCAACCCTGGTGCTGATGGACAGCCTGGTGCTAAAGGAGCCAATGGCGCT
CCTGGTATTGCTGGTGCTCCTGGCTTCCCTGGTGCCCGAGGCCCCTCTGGACCCC
AGGGCCCCAGCGGCCCCCCTGGCCCCAAGGGTAACAGCGGTGAACCTGGTGCTCC
TGGCAGCAAAGGAGACACTGGCGCCAAGGGAGAACCCGGTCCCACTGGTATTCAA
GGCCCCCCTGGCCCCGCTGGGGAAGAAGGAAAGCGAGGAGCCCGAGGTGAACCTG
GACCTGCTGGCCTGCCTGGACCCCCTGGCGAGCGTGGTGGACCTGGAAGCCGTGG
TTTCCCTGGCGCCGACGGTGTTGCTGGTCCCAAGGGTCCTGCTGGTGAACGCGGT
GCTCCTGGCCCTGCTGGCCCCAAAGGTTCTCCTGGTGAAGCTGGTCGCCCCGGTG
AAGCTGGTCTGCCCGGTGCCAAGGGTCTGACTGGAAGCCCTGGCAGCCCGGGTCC
TGATGGCAAAACTGGCCCCCCTGGTCCCGCCGGTCAAGATGGCCGCCCTGGACCT
CCAGGCCCTCCCGGTGCCCGTGGTCAGGCTGGCGTGATGGGTTTCCCTGGACCTA
AAGGTGCTGCTGGAGAGCCTGGAAAAGCTGGAGAGCGAGGTGTTCCTGGACCCCC
TGGCGCTGTTGGTCCTGCTGGCAAAGACGGAGAAGCTGGAGCTCAGGGACCCCCA
GGACCTGCTGGCCCGCTGGTGAGAGAGGCGAACAAGGCCCTGCTGGCTCCCCTGG
ATTCCAGGGTCTCCCCGGCCCTGCTGGTCCTCCTGGTGAAGCAGGCAAACCTGGT
GAACAGGGTGTTCCTGGAGATCTTGGTGCCCCCGGCCCCTCTGGAGCAAGAGGCG
AGAGAGGTTTCCCCGGCGAGCGTGGTGTGCAAGGGCCGCCCGGTCCTGCAGGTCC

*Figure 1A*

1

```
CCGTGGGGCCAATGGTGCCCCTGGCAACGATGGTGCTAAGGGTGATGCTGGTGCC
CCTGGAGCCCCCGGTAGCCAGGGTGCCCCTGGCCTTCAAGGAATGCCTGGTGAAC
GAGGTGCAGCTGGTCTTCCAGGCCCTAAGGGTGACAGAGGGGATGCTGGTCCCAA
AGGTGCTGATGGTGCTCCTGGCAAAGATGGCGTCCGTGGTCTGACTGGTCCCATC
GGTCCTCCTGGCCCCGCTGGTGCCCCTGGTGACAAGGGTGAAGCTGGTCCTAGCG
GCCCAGCCGGTCCCACTGGAGCTCGTGGTGCCCCCGGTGACCGTGGTGAGCCTGG
TCCCCCCGGCCCTGCTGGCTTCGCTGGCCCCCCTGGTGCTGATGGCCAACCTGGT
GCTAAAGGCGAACCTGGTGATGCTGGTGCTAAAGGTGACGCTGGTCCCCCCGGCC
CTGCTGGGCCCGCTGGACCCCCGGCCCCATTGGTAACGTTGGTGCTCCCGGACC
CAAAGGTGCTCGTGGCAGCGCTGGTCCCCCTGGTGCTACTGGTTTCCAGGTGCT
GCTGGCCGAGTTGGTCCCCCCGGCCCCTCTGGAAATGCTGGACCCCCTGGCCCTC
CTGGCCCTGCTGGCAAAGAAGGCAGCAAAGGCCCCCGCGGTGAGACTGGCCCCGC
TGGGCGTCCCGGTGAAGTCGGTCCCCCTGGTCCCCCTGGCCCCGCTGGTGAGAAA
GGAGCCCCTGGTGCTGACGGACCTGCTGGAGCTCCTGGCACTCCTGGACCTCAAG
GTATTGCTGGACAGCGTGGTGTGGTCGGCCTGCCTGGTCAGAGAGGAGAAAGAGG
CTTCCCTGGTCTTCCTGGCCCCTCTGGTGAACCCGGCAAACAAGGTCCTTCTGGA
GCAAGTGGTGAACGTGGCCCCCCTGGTCCCATGGGCCCCCCTGGATTGGCTGGAC
CCCCTGGCGAGTCTGGACGTGAGGGAGCTCCTGGTGCTGAAGGATCCCCTGGACG
AGATGGTTCTCCTGGCGCCAAGGGTGACCGTGGTGAGACCGGCCCTGCTGGACCT
CCTGGTGCTCCTGGCGCTCCCGGTGCCCCCGGCCCTGTCGGACCTGCCGGCAAGA
GCGGTGATCGTGGTGAGACCGGTCCTGCTGGTCCTGCTGGTCCCATTGGCCCCGT
TGGTGCCCGTGGCCCCGCTGGACCCCAAGGCCCCGTGGTGACAAGGGTGAGACA
GGCGAACAGGGCGACAGAGGCATTAAGGGTCACCGTGGCTTCTCTGGTCTCCAGG
GTCCCCCCGGCCCTCCCGGCTCTCCTGGTGAGCAAGGTCCTTCCGGAGCCTCTGG
TCCTGCTGGTCCCCGCGGTCCCCCTGGCTCTGCTGGTTCTCCCGGCAAAGATGGA
CTCAATGGTCTCCCAGGCCCCATCGGTCCCCCTGGGCCTCGAGGTCGCACTGGTG
ATGCTGGTCCTGCTGGTCCTCCCGGCCCTCCTGGACCCCCTGGTCCCCCAGGTCC
TCCCAGCGGCGGCTACGACTTGAGCTTCCTGCCCCAGCCACCTCAAGAGAAGGCT
CACGATGGTGGCCGCTACTACCGGGCTGATGATGCCAATGTGGTCCGTGACCGTG
ACCTCGAGGTGGACACCACCCTCAAGAGCCTGAGCCAGCAGATCGAGAACATCCG
GAGCCCTGAAGGCAGCCGCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATG
TGCCACTCTGACTGGAAGAGCGGAGAATACTGGATTGACCCCAACCAAGGCTGCA
ACCTGGATGCCATTAAGGTCTTCTGCAACATGGAAACCGGTGAGACCTGTGTATA
CCCCACTCAGCCCAGCGTGGCCCAGAAGAACTGGTATATCAGCAAGAACCCCAAG
GAAAAGAGGCACGTCTGGTACGGCGAGAGCATGACCGGCGGATTCCAGTTCGAGT
ATGGCGGCCAGGGGTCCGATCCTGCCGATGTGGCCATCCAGCTGACTTTCCTGCG
CCTGATGTCCACCGAGGCCTCCCAGAACATCACCTACCACTGCAAGAACAGCGTG
GCCTACATGGACCAGCAGACTGGCAACCTCAAGAAGGCCCTGCTCCTCCAGGGCT
CCAACGAGATCGAGATCCGGGCCGAGGGCAACAGCCGCTTCACCTACAGCGTCAC
CTACGATGGCTGCACGAGTCACACCGGAGCCTGGGGCAAGACAGTGATCGAATAC
AAAACCACCAAGACCTCCCGCTTGCCCATCATCGATGTGGCCCCCTTGGACGTTG
```

Figure 1B

GCGCCCCAGACCAGGAATTCGGTTTCGACGTTGGCCCTGCCTGCTTCCTGTAAAC
TCCTTCCACCCCAACCTGGCTCCCTCCCACCCAACCCACTTGCCCCTGACTCTGG
AAACAGACAAACAACCCAAACTGAAACCCCCGAAAAGCCAAAAAATGGGAGACAA
TTTCACATGGACTTTGGAAAATATTTTTTTCCTTTGCATTCATCTCTCAAACTTA
GTTTTTATCTTTGACCAACTGAACATGACCAAAAACCAAAAGTGCATTCAACCTT
ACCAAAAAAAAAAAAAAAA

Figure 1C

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Ala
Ala Thr Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Glu
Glu Gly Gln Glu Glu Asp Ile Pro Pro Val Thr Cys Val Gln
Asn Gly Leu Arg Tyr His Asp Arg Asp Val Trp Lys Pro Val
Pro Cys Gln Ile Cys Val Cys Asp Asn Gly Asn Val Leu Cys
Asp Asp Val Ile Cys Asp Glu Leu Lys Asp Cys Pro Asn Ala
Lys Val Pro Thr Asp Glu Cys Cys Pro Val Cys Pro Glu Gly
Gln Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly
Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala
Gly Pro Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu
Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
Leu Gly Gly Asn Phe Ala Pro Gln Leu Ser Tyr Gly Tyr Asp
Glu Lys Ser Thr Gly Ile Ser Val Pro Gly Pro Met Gly Pro
Ser Gly Pro Arg Gly Leu Pro Gly Pro Pro Gly Ala Pro Gly
Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro Gly Glu Pro
Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly Pro
Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly
Arg Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg
Gly Leu Pro Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His
Arg Gly Phe Ser Gly Leu Asp Gly Ala Lys Gly Asp Ala Gly
Pro Ala Gly Pro Lys Gly Glu Pro Gly Ser Pro Gly Glu Asn
Gly Ala Pro Gly Gln Met Gly Pro Arg Gly Leu Pro Gly Glu
Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly
Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro Thr
Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala
Lys Gly Glu Gly Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly

Figure 2A                                         1

Pro Gln Gly Val Arg Gly Glu Pro Gly Pro Gly Pro Ala
Gly Ala Ala Gly Pro Ala Gly Asn Pro Gly Ala Asp Gly Gln
Pro Gly Ala Lys Gly Ala Asn Gly Ala Pro Gly Ile Ala Gly
Ala Pro Gly Phe Pro Gly Ala Arg Gly Pro Ser Gly Pro Gln
Gly Pro Ser Gly Pro Pro Gly Pro Lys Gly Asn Ser Gly Glu
Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys Gly
Glu Pro Gly Pro Thr Gly Ile Gln Gly Pro Pro Gly Pro Ala
Gly Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro
Ala Gly Leu Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly
Ser Arg Gly Phe Pro Gly Ala Asp Gly Val Ala Gly Pro Lys
Gly Pro Ala Gly Glu Arg Gly Ala Pro Gly Pro Ala Gly Pro
Lys Gly Ser Pro Gly Glu Ala Gly Arg Pro Gly Glu Ala Gly
Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro Gly Ser Pro
Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly Gln
Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly
Gln Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala
Gly Glu Pro Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro
Pro Gly Ala Val Gly Pro Ala Gly Lys Asp Gly Glu Ala Gly
Ala Gln Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly Glu Arg
Gly Glu Gln Gly Pro Ala Gly Ser Pro Gly Phe Gln Gly Leu
Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly Lys Pro Gly
Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro Ser
Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val
Gln Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly
Ala Pro Gly Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro
Gly Ala Pro Gly Ser Gln Gly Ala Pro Gly Leu Gln Gly Met
Pro Gly Glu Arg Gly Ala Ala Gly Leu Pro Gly Pro Lys Gly

Figure 2B

2

Asp Arg Gly Asp Ala Gly Pro Lys Gly Ala Asp Gly Ala Pro
Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro Ile Gly Pro
Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ala Gly
Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro
Gly Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe
Ala Gly Pro Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly
Glu Pro Gly Asp Ala Gly Ala Lys Gly Asp Ala Gly Pro Pro
Gly Pro Ala Gly Pro Ala Gly Pro Pro Gly Pro Ile Gly Asn
Val Gly Ala Pro Gly Pro Lys Gly Ala Arg Gly Ser Ala Gly
Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala Gly Arg Val
Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly Pro
Pro Gly Pro Ala Gly Lys Glu Gly Ser Lys Gly Pro Arg Gly
Glu Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro
Gly Pro Pro Gly Pro Ala Gly Glu Lys Gly Ala Pro Gly Ala
Asp Gly Pro Ala Gly Ala Pro Gly Thr Pro Gly Pro Gln Gly
Ile Ala Gly Gln Arg Gly Val Val Gly Leu Pro Gly Gln Arg
Gly Glu Arg Gly Phe Pro Gly Leu Pro Gly Pro Ser Gly Glu
Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly Glu Arg Gly
Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro Pro
Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser
Pro Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly
Glu Thr Gly Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro
Gly Ala Pro Gly Pro Val Gly Pro Ala Gly Lys Ser Gly Asp
Arg Gly Glu Thr Gly Pro Ala Gly Pro Ala Gly Pro Ile Gly
Pro Val Gly Ala Arg Gly Pro Ala Gly Pro Gln Gly Pro Arg
Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp Arg Gly Ile
Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro Gly

Figure 2C                                3

Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser

Gly Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ser

Pro Gly Lys Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly

Pro Pro Gly Pro Arg Gly Arg Thr Gly Asp Ala Gly Pro Ala

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro

Pro Ser Gly Gly Tyr Asp Leu Ser Phe Leu Pro Gln Pro Pro

Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr Arg Ala Asp

Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp Thr

Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser

Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp

Leu Lys Met Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp

Ile Asp Pro Asn Gln Gly Cys Asn Leu Asp Ala Ile Lys Val

Phe Cys Asn Met Glu Thr Gly Glu Thr Cys Val Tyr Pro Thr

Gln Pro Ser Val Ala Gln Lys Asn Trp Tyr Ile Ser Lys Asn

Pro Lys Glu Lys Arg His Val Trp Tyr Gly Glu Ser Met Thr

Gly Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp Pro

Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser

Thr Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser

Val Ala Tyr Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala

Leu Leu Leu Gln Gly Ser Asn Glu Ile Glu Ile Arg Ala Glu

Gly Asn Ser Arg Phe Thr Tyr Ser Val Thr Tyr Asp Gly Cys

Thr Ser His Thr Gly Ala Trp Gly Lys Thr Val Ile Glu Tyr

Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile Ile Asp Val Ala

Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe Asp

Val Gly Pro Ala Cys Phe Leu

Figure 2D

4

GAATTCAGGGACATGATGAGCTTTGTGCAAAAGGGGACCTGGTTACTTTTCGCTC
TGCTTCATCCCACTGTTATTTTGGCACAACAGGAAGCTGTTGACGGAGGATGCTC
CCATCTCGGTCAGTCTTATGCAGATAGAGATGTATGGAAACCAGAACCGTGCCAA
ATATGCGTCTGTGACTCAGGATCCGTTCTCTGTGATGACATAATATGTGACGACC
AAGAATTAGACTGCCCCAACCCTGAAATCCCGTTTGGAGAATGTTGTGCAGTTTG
CCCACAGCCTCCAACAGCTCCCACTCGCCCTCCTAATGGTCAAGGACCTCAAGGC
CCCAAGGGAGATCCAGGTCCTCCTGGTATTCCTGGGCGAAATGGCGATCCTGGTC
CTCCAGGATCACCAGGCTCCCCAGGTTCTCCCGGCCCTCCTGGAATCTGTGAATC
ATGTCCTACTGGTGGCCAGAACTATTCTCCCCAGTACGAAGCATATGATGTCAAG
TCTGGAGTAGCAGGAGGAGGAATCGCAGGCTATCCTGGGCCAGCTGGTCCTCCTG
GCCCACCCGGACCCCCTGGCACATCTGGCCATCCTGGTGCCCCTGGCGCTCCAGG
ATACCAAGGTCCCCCCGGTGAACCTGGGCAAGCTGGTCCGGCAGGTCCTCCAGGA
CCTCCTGGTGCTATAGGTCCATCTGGCCCTGCTGGAAAAGATGGGGAATCAGGAA
GACCCGGACGACCTGGAGAGCGAGGATTTCCTGGCCCTCCTGGTATGAAAGGCCC
AGCTGGTATGCCTGGATTCCCTGGTATGAAAGGACACAGAGGCTTTGATGGACGA
AATGGAGAGAAAGGCGAAACTGGTGCTCCTGGATTAAAGGGGGAAAATGGCGTTC
CAGGTGAAAATGGAGCTCCTGGACCCATGGGTCCAAGAGGGGCTCCCGGTGAGAG
AGGACGGCCAGGACTTCCTGGAGCCGCAGGGGCTCGAGGTAATGATGGAGCTCGA
GGAAGTGATGGACAACCGGGCCCCCCTGGTCCTCCTGGAACTGCAGGATTCCCTG
GTTCCCCTGGTGCTAAGGGTGAAGTTGGACCTGCAGGATCTCCTGGTTCAAGTGG
CGCCCCTGGACAAAGAGGAGAACCTGGACCTCAGGGACATGCTGGTGCTCCAGGT
CCCCCTGGGCCTCCTGGGAGTAATGGTAGTCCTGGTGGCAAAGGTGAAATGGGTC
CTGCTGGCATTCCTGGGGCTCCTGGGCTGATAGGAGCTCGTGGTCCTCCAGGGCC
ACCTGGCACCAATGGTGTTCCCGGGCAACGAGGTGCTGCAGGTGAACCCGGTAAG
AATGGAGCCAAAGGAGACCCAGGACCACGTGGGGAACGCGGAGAAGCTGGTTCTC
CAGGTATCGCAGGACCTAAGGGTGAAGATGGCAAAGATGGTTCTCCTGGAGAACC
TGGTGCAAATGGACTTCCTGGAGCTGCAGGAGAAAGGGGTGTGCCTGGATTCCGA
GGACCTGCTGGAGCAAATGGCCTTCCAGGAGAAAAGGGTCCTCCTGGGGACCGTG
GTGGCCCAGGCCCTGCAGGGCCCAGAGGTGTTGCTGGAGAGCCCGGCAGAGATGG
TCTCCCTGGAGGTCCAGGATTGAGGGGTATTCCTGGTAGCCCGGGAGGACCAGGC
AGTGATGGGAAACCAGGGCCTCCTGGAAGCCAAGGAGAGACGGGTCGACCCGGTC
CTCCAGGTTCACCTGGTCCGCGAGGCCAGCCTGGTGTCATGGGCTTCCCTGGTCC
CAAAGGAAACGATGGTGCTCCTGGAAAAAATGGAGAACGAGGTGGCCCTGGAGGT
CCTGGCCCTCAGGGTCCTGCTGGAAAGAATGGTGAGACCGGACCTCAGGGTCCTC
CAGGACCTACTGGCCCTTCTGGTGACAAAGGAGACACAGGACCCCCTGGTCCACA
AGGACTACAAGGCTTGCCTGGAACGAGTGGTCCCCCAGGAGAAAACGGAAAACCT
GGTGAACCTGGTCCAAAGGGTGAGGCTGGTGCACCTGGAATTCCAGGAGGCAAGG
GTGATTCTGGTGCTCCCGGTGAACGCGGACCTCCTGGAGCAGGAGGGCCCCCTGG
ACCTAGAGGTGGAGCTGGCCCCCCTGGTCCCGAAGGAGGAAAGGGTGCTGCTGGT

*Figure 3 A*                                                    1

CCCCCTGGGCCACCTGGTTCTGCTGGTACACCTGGTCTGCAAGGAATGCCTGGAG
AAAGAGGGGGTCCTGGAGGCCCTGGTCCAAAGGGTGATAAGGGTGAGCCTGGCAG
CTCAGGTGTCGATGGTGCTCCAGGGAAAGATGGTCCACGGGGTCCCACTGGTCCC
ATTGGTCCTCCTGGCCCAGCTGGTCAGCCTGGAGATAAGGGTGAAAGTGGTGCCC
CTGGAGTTCCGGGTATAGCTGGTCCTCGCGGTGGCCCTGGTGAGAGAGGCGAACA
GGGGCCCCCAGGACCTGCTGGCTTCCCTGGTGCTCCTGGCCAGAATGGTGAGCCT
GGTGCTAAAGGAGAAAGAGGCGCTCCTGGTGAGAAAGGTGAAGGAGGCCCTCCCG
GAGCCGCAGGACCCGCCGGAGGTTCTGGGCCTGCCGGTCCCCCAGGCCCCCAAGG
TGTCAAAGGCGAACGTGGCAGTCCTGGTGGTCCTGGTGCTGCTGGCTTCCCCGGT
GGTCGTGGTCCTCCTGGCCCTCCTGGCAGTAATGGTAACCCAGGCCCCCCAGGCT
CCAGTGGTGCTCCAGGCAAAGATGGTCCCCCAGGTCCACCTGGCAGTAATGGTGC
TCCTGGCAGCCCCGGGATCTCTGGACCAAAGGGTGATTCTGGTCCACCAGGTGAG
AGGGGAGCACCTGGCCCCCAGGGGCCTCCGGGAGCTCCAGGCCCACTAGGAATTG
CAGGACTTACTGGAGCACGAGGTCTTGCAGGCCCACCAGGCATGCCAGGTGCTAG
GGGCAGCCCCGGCCCACAGGGCATCAAGGGTGAAAATGGTAAACCAGGACCTAGT
GGTCAGAATGGAGAACGTGGTCCTCCTGGCCCCCAGGGTCTTCCTGGTCTGGCTG
GTACAGCTGGTGAGCCTGGAAGAGATGGAAACCCTGGATCAGATGGTCTGCCAGG
CCGAGATGGAGCGCCAGGTGCCAAGGGTGACCGTGGTGAAAATGGCTCTCCTGGT
GCCCCTGGAGCTCCTGGTCACCCAGGCCCTCCTGGTCCTGTCGGTCCAGCTGGAA
AGAGCGGTGACAGAGGAGAAACTGGCCCTGCTGGTCCTTCTGGGGCCCCCGGTCC
TGCCGGATCAAGAGGTCCTCCTGGTCCCCAAGGCCCACGCGGTGACAAAGGGGAA
ACCGGTGAGCGTGGTGCTATGGGCATCAAAGGACATCGCGGATTCCCTGGCAACC
CAGGGGCCCCCGGATCTCCGGGTCCCGCTGGTCATCAAGGTGCAGTTGGCAGTCC
AGGCCCTGCAGGCCCCAGAGGACCTGTTGGACCTAGCGGGCCCCCTGGAAAGGAC
GGAGCAAGTGGACACCCTGGTCCCATTGGACCACCGGGGCCCCGAGGTAACAGAG
GTGAAAGAGGATCTGAGGGCTCCCCAGGCCACCCAGGACAACCAGGCCCTCCTGG
ACCTCCTGGTGCCCCTGGTCCATGTTGTGGTGCTGGCGGGGTTGCTGCCATTGCT
GGTGTTGGAGCCGAAAAAGCTGGTGGTTTTGCCCCATATTATGGAGATGAACCGA
TAGATTTCAAAATCAATACCGATGAGATTATGACCTCACTCAAATCAGTCAATGG
ACAAATAGAAAGCCTCATTAGTCCTGATGGTTCCCGTAAAAACCCTGCACGGAAC
TGCAGGGACCTGAAATTCTGCCATCCTGAACTCCAGAGTGGAGAATATTGGGTTG
ATCCTAACCAAGGTTGCAAATTGGATGCTATTAAAGTCTACTGTAACATGGAAAC
TGGGGAAACGTGCATAAGTGCCAGTCCTTTGACTATCCCACAGAAGAACTGGTGG
ACAGATTCTGGTGCTGAGAAGAAACATGTTTGGTTTGGAGAATCCATGGAGGGTG
GTTTTCAGTTTAGCTATGGCAATCCTGAACTTCCCGAAGACGTCCTCGATGTCCA
GCTGGCATTCCTCCGACTTCTCTCCAGCCGGGCCTCTCAGAACATCACATATCAC
TGCAAGAATAGCATTGCATACATGGATCATGCCAGTGGGAATGTAAAGAAAGCCT
TGAAGCTGATGGGGTCAAATGAAGGTGAATTCAAGGCTGAAGGAAATAGCAAATT
CACATACACAGTTCTGGAGGATGGTTGCACAAAACACACTGGGGAATGGGGCAAA
ACAGTCTTCCAGTATCAAACACGCAAGGCCGTCAGACTACCTATTGTAGATATTG

*Figure 3B*

2

CACCCTATGATATCGGTGGTCCTGATCAAGAATTTGGTGCGGACATTGGCCCTGT
TTGCTTTTTATAAACCAAACCTGAATTC

Figure 3C

3

Met Met Ser Phe Val Gln Lys Gly Thr Trp Leu Leu Phe Ala

Leu Leu His Pro Thr Val Ile Leu Ala Gln Gln Glu Ala Val

Asp Gly Gly Cys Ser His Leu Gly Gln Ser Tyr Ala Asp Arg

Asp Val Trp Lys Pro Glu Pro Cys Gln Ile Cys Val Cys Asp

Ser Gly Ser Val Leu Cys Asp Asp Ile Ile Cys Asp Asp Gln

Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro Phe Gly Glu Cys

Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr Arg Pro

Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly

Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Pro Pro

Gly Ser Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile

Cys Glu Ser Cys Pro Thr Gly Gly Gln Asn Tyr Ser Pro Gln

Tyr Glu Ala Tyr Asp Val Lys Ser Gly Val Ala Gly Gly Gly

Ile Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly Pro Pro

Gly Pro Pro Gly Thr Ser Gly His Pro Gly Ala Pro Gly Ala

Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala Gly

Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser

Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg

Pro Gly Glu Arg Gly Phe Pro Gly Pro Pro Gly Met Lys Gly

Pro Ala Gly Met Pro Gly Phe Pro Gly Met Lys Gly His Arg

Gly Phe Asp Gly Arg Asn Gly Glu Lys Gly Glu Thr Gly Ala

Pro Gly Leu Lys Gly Glu Asn Gly Val Pro Gly Glu Asn Gly

Ala Pro Gly Pro Met Gly Pro Arg Gly Ala Pro Gly Glu Arg

Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly Asn

Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly

Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys

Gly Glu Val Gly Pro Ala Gly Ser Pro Gly Ser Ser Gly Ala

Figure 4A                                    |

Pro Gly Gln Arg Gly Glu Pro Gly Pro Gln Gly His Ala Gly
Ala Pro Gly Pro Pro Gly Pro Pro Gly Ser Asn Gly Ser Pro
Gly Gly Lys Gly Glu Met Gly Pro Ala Gly Ile Pro Gly Ala
Pro Gly Leu Ile Gly Ala Arg Gly Pro Pro Gly Pro Pro Gly
Thr Asn Gly Val Pro Gly Gln Arg Gly Ala Ala Gly Glu Pro
Gly Lys Asn Gly Ala Lys Gly Asp Pro Gly Pro Arg Gly Glu
Arg Gly Glu Ala Gly Ser Pro Gly Ile Ala Gly Pro Lys Gly
Glu Asp Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn
Gly Leu Pro Gly Ala Ala Gly Glu Arg Gly Val Pro Gly Phe
Arg Gly Pro Ala Gly Ala Asn Gly Leu Pro Gly Glu Lys Gly
Pro Pro Gly Asp Arg Gly Gly Pro Gly Pro Ala Gly Pro Arg
Gly Val Ala Gly Glu Pro Gly Arg Asp Gly Leu Pro Gly Gly
Pro Gly Leu Arg Gly Ile Pro Gly Ser Pro Gly Gly Pro Gly
Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Thr
Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly Gln
Pro Gly Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly
Ala Pro Gly Lys Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro
Gly Pro Gln Gly Pro Ala Gly Lys Asn Gly Glu Thr Gly Pro
Gln Gly Pro Pro Gly Pro Thr Gly Pro Ser Gly Asp Lys Gly
Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu Gln Gly Leu Pro
Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu
Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro Gly
Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro Pro
Gly Ala Gly Gly Pro Pro Gly Pro Arg Gly Gly Ala Gly Pro
Pro Gly Pro Glu Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly
Pro Pro Gly Ser Ala Gly Thr Pro Gly Leu Gln Gly Met Pro
Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Lys Gly Asp

Figure 4B                                                           2

Lys Gly Glu Pro Gly Ser Ser Gly Val Asp Gly Ala Pro Gly

Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly Pro Pro

Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Ser Gly Ala

Pro Gly Val Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro Gly

Glu Arg Gly Glu Gln Gly Pro Pro Gly Pro Ala Gly Phe Pro

Gly Ala Pro Gly Gln Asn Gly Glu Pro Gly Ala Lys Gly Glu

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly

Ala Ala Gly Pro Ala Gly Gly Ser Gly Pro Ala Gly Pro Pro

Gly Pro Gln Gly Val Lys Gly Glu Arg Gly Ser Pro Gly Gly

Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly Pro Pro Gly

Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser Ser

Gly Ala Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly Ser

Asn Gly Ala Pro Gly Ser Pro Gly Ile Ser Gly Pro Lys Gly

Asp Ser Gly Pro Pro Gly Glu Arg Gly Ala Pro Gly Pro Gln

Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile Ala Gly Leu

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly

Ala Arg Gly Ser Pro Gly Pro Gln Gly Ile Lys Gly Glu Asn

Gly Lys Pro Gly Pro Ser Gly Gln Asn Gly Glu Arg Gly Pro

Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly

Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro

Gly Arg Asp Gly Ala Pro Gly Ala Lys Gly Asp Arg Gly Glu

Asn Gly Ser Pro Gly Ala Pro Gly Ala Pro Gly His Pro Gly

Pro Pro Gly Pro Val Gly Pro Ala Gly Lys Ser Gly Asp Arg

Gly Glu Thr Gly Pro Ala Gly Pro Ser Gly Ala Pro Gly Pro

Ala Gly Ser Arg Gly Pro Pro Gly Pro Gln Gly Pro Arg Gly

Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Met Gly Ile Lys

Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser

3

Figure 4 C

```
Pro Gly Pro Ala Gly His Gln Gly Ala Val Gly Ser Pro Gly
Pro Ala Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro
Gly Lys Asp Gly Ala Ser Gly His Pro Gly Pro Ile Gly Pro
Pro Gly Pro Arg Gly Asn Arg Gly Glu Arg Gly Ser Glu Gly
Ser Pro Gly His Pro Gly Gln Pro Gly Pro Pro Gly Pro Pro
Gly Ala Pro Gly Pro Cys Cys Gly Ala Gly Gly Val Ala Ala
Ile Ala Gly Val Gly Ala Glu Lys Ala Gly Gly Phe Ala Pro
Tyr Tyr Gly Asp Glu Pro Ile Asp Phe Lys Ile Asn Thr Asp
Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu
Ser Leu Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg
Asn Cys Arg Asp Leu Lys Phe Cys His Pro Glu Leu Gln Ser
Gly Glu Tyr Trp Val Asp Pro Asn Gln Gly Cys Lys Leu Asp
Ala Ile Lys Val Tyr Cys Asn Met Glu Thr Gly Glu Thr Cys
Ile Ser Ala Ser Pro Leu Thr Ile Pro Gln Lys Asn Trp Trp
Thr Asp Ser Gly Ala Glu Lys Lys His Val Trp Phe Gly Glu
Ser Met Glu Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg
Leu Leu Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys
Lys Asn Ser Ile Ala Tyr Met Asp His Ala Ser Gly Asn Val
Lys Lys Ala Leu Lys Leu Met Gly Ser Asn Glu Gly Glu Phe
Lys Ala Glu Gly Asn Ser Lys Phe Thr Tyr Thr Val Leu Glu
Asp Gly Cys Thr Lys His Thr Gly Glu Trp Gly Lys Thr Val
Phe Gln Tyr Gln Thr Arg Lys Ala Val Arg Leu Pro Ile Val
Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
Gly Ala Asp Ile Gly Pro Val Cys Phe Leu
```

Figure 4D                                                          4

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GAATTCAGGGACATGATGAGCTTTGTGCAAAAGGGGACCTGGTTACTTTTCGCTC
TGCTTCATCCCACTGTTATTTTGGCACAACAGGAAGCTGTTGACGGAGGATGCTC
CCATCTCGGTCAGTCTTATGCAGATAGAGATGTATGGAAACCAGAACCGTGCCAA
ATATGCGTCTGTGACTCAGGATCCGTTCTCTGTGATGACATAATATGTGACGACC
AAGAATTAGACTGCCCCAACCCTGAAATCCCGTTTGGAGAATGTTGTGCAGTTTG
CCCACAGCCTCCAACAGCTCCCACTCGCCCTCCTAATGGTCAAGGACCTCAAGGC
CCCAAGGGAGATCCAGGTCCTCCTGGTATTCCTGGGCGAAATGGCGATCCTGGTC
CTCCAGGATCACCAGGCTCCCCAGGTTCTCCCGGCCCTCCTGGAATCTGTGAATC
ATGTCCTACTGGTGGCCAGAACTATTCTCCCCAGTACGAAGCATATGATGTCAAG
TCTGGAGTAGCAGGAGGAGGAATCGCAGGCTATCCTGGGCCAGCTGGTCCTCCTG
GCCCACCCGGACCCCCTGGCACATCTGGCCATCCTGGTGCCCCTGGCGCTCCAGG
ATACCAAGGTCCCCCCGGTGAACCTGGGCAAGCTGGTCCGGCAGGTCCTCCAGGA
CCTCCTGGTGCTATAGGTCCATCTGGCCCTGCTGGAAAAGATGGGGAATCAGGAA
GACCCGGACGACCTGGAGAGCGAGGATTTCCTGGCCCTCCTGGTATGAAAGGCCC
AGCTGGTATGCCTGGATTCCCTGGTATGAAAGGACACAGAGGCTTTGATGGACGA
AATGGAGAGAAAGGCGAAACTGGTGCTCCTGGATTAAAGGGGGAAAATGGCGTTC
CAGGTGAAAATGGAGCTCCTGGACCCATGGGTCCAAGAGGGGCTCCCGGTGAGAG
AGGACGGCCAGGACTTCCTGGAGCCGCAGGGGCTCGAGGTAATGATGGAGCTCGA
GGAAGTGATGGACAACCGGGCCCCCCTGGTCCTCCTGGAACTGCAGGATTCCCTG
GTTCCCCTGGTGCTAAGGGTGAAGTTGGACCTGCAGGATCTCCTGGTTCAAGTGG
CGCCCCTGGACAAAGAGGAGAACCTGGACCTCAGGGACATGCTGGTGCTCCAGGT
CCCCCTGGGCCTCCTGGGAGTAATGGTAGTCCTGGTGGCAAAGGTGAAATGGGTC
CTGCTGGCATTCCTGGGGCTCCTGGGCTGATAGGAGCTCGTGGTCCTCCAGGGCC
ACCTGGCACCAATGGTGTTCCCGGGCAACGAGGTGCTGCAGGTGAACCCGGTAAG
AATGGAGCCAAAGGAGACCCAGGACCACGTGGGGAACGCGGAGAAGCTGGTTCTC
CAGGTATCGCAGGACCTAAGGGTGAAGATGGCAAAGATGGTTCTCCTGGAGAACC
TGGTGCAAATGGACTTCCTGGAGCTGCAGGAGAAAGGGGTGTGCCTGGATTCCGA
GGACCTGCTGGAGCAAATGGCCTTCCAGGAGAAAAGGGTCCTCCTGGGGACCGTG
GTGGCCCAGGCCCTGCAGGGCCCAGAGGTGTTGCTGGAGAGCCCGGCAGAGATGG
TCTCCCTGGAGGTCCAGGATTGAGGGGTATTCCTGGTAGCCCGGGAGGACCAGGC
AGTGATGGGAAACCAGGGCCTCCTGGAAGCCAAGGAGAGACGGGTCGACCCGGTC
CTCCAGGTTCACCTGGTCCGCGAGGCCAGCCTGGTGTCATGGGCTTCCCTGGTCC
CAAAGGAAACGATGGTGCTCCTGGAAAAAATGGAGAACGAGGTGGCCCTGGAGGT
CCTGGCCCTCAGGGTCCTGCTGGAAAGAATGGTGAGACCGGACCTCAGGGTCCTC
CAGGACCTACTGGCCCTTCTGGTGACAAAGGAGACACAGGACCCCCTGGTCCACA
AGGACTACAAGGCTTGCCTGGAACGAGTGGTCCCCCAGGAGAAAACGGAAAAACCT
GGTGAACCTGGTCCAAAGGGTGAGGCTGGTGCACCTGGAATTCCAGGAGGCAAGG
GTGATTCTGGTGCTCCCGGTGAACGCGGACCTCCTGGAGCAGGAGGGCCCCCTGG
ACCTAGAGGTGGAGCTGGCCCCCCTGGTCCCGAAGGAGGAAAGGGTGCTGCTGGT
```

Figure 5A

```
CCCCCTGGGCCACCTGGTTCTGCTGGTACACCTGGTCTGCAAGGAATGCCTGGAG
AAAGAGGGGGTCCTGGAGGCCCTGGTCCAAAGGGTGATAAGGGTGAGCCTGGCAG
CTCAGGTGTCGATGGTGCTCCAGGGAAAGATGGTCCACGGGGTCCCACTGGTCCC
ATTGGTCCTCCTGGCCCAGCTGGTCAGCCTGGAGATAAGGGTGAAAGTGGTGCCC
CTGGAGTTCCGGGTATAGCTGGTCCTCGCGGTGGCCCTGGTGAGAGAGGCGAACA
GGGGCCCCCAGGACCTGCTGGCTTCCCTGGTGCTCCTGGCCAGAATGGTGAGCCT
GGTGCTAAAGGAGAAAGAGGCGCTCCTGGTGAGAAAGGTGAAGGAGGCCCTCCCG
GAGCCGCAGGACCCGCCGGAGGTTCTGGGCCTGCCGGTCCCCCAGGCCCCCAAGG
TGTCAAAGGCGAACGTGGCAGTCCTGGTGGTCCTGGTGCTGCTGGCTTCCCCGGT
GGTCGTGGTCCTCCTGGCCCTCCTGGCAGTAATGGTAACCCAGGCCCCCCAGGCT
CCAGTGGTGCTCCAGGCAAAGATGGTCCCCCAGGTCCACCTGGCAGTAATGGTGC
TCCTGGCAGCCCCGGGATCTCTGGACCAAAGGGTGATTCTGGTCCACCAGGTGAG
AGGGGAGCACCTGGCCCCCAGGGGCCTCCGGGAGCTCCAGGCCCACTAGGAATTG
CAGGACTTACTGGAGCACGAGGTCTTGCAGGCCCACCAGGCATGCCAGGTGCTAG
GGGCAGCCCCGGCCCACAGGGCATCAAGGGTGAAAATGGTAAACCAGGACCTAGT
GGTCAGAATGGAGAACGTGGTCCTCCTGGCCCCCAGGGTCTTCCTGGTCTGGCTG
GTACAGCTGGTGAGCCTGGAAGAGATGGAAACCCTGGATCAGATGGTCTGCCAGG
CCGAGATGGAGCGCCAGGTGCCAAGGGTGACCGTGGTGAAAATGGCTCTCCTGGT
GCCCCTGGAGCTCCTGGTCACCCAGGCCCTCCTGGTCCTGTCGGTCCAGCTGGAA
AGAGCGGTGACAGAGGAGAAACTGGCCCTGCTGGTCCTTCTGGGGCCCCCGGTCC
TGCCGGATCAAGAGGTCCTCCTGGTCCCCAAGGCCCACGCGGTGACAAAGGGGAA
ACCGGTGAGCGTGGTGCTATGGGCATCAAAGGACATCGCGGATTCCCTGGCAACC
CAGGGGCCCCCGGATCTCCGGGTCCCGCTGGTCATCAAGGTGCAGTTGGCAGTCC
AGGCCCTGCAGGCCCCAGAGGACCTGTTGGACCTAGCGGGCCCCCTGGAAAGGAC
GGAGCAAGTGGACACCCTGGTCCCATTGGACCACCGGGGCCCCGAGGTAACAGAG
GTGAAAGAGGATCTGAGGGCTCCCCAGGCCACCCAGGACAACCAGGCCCTCCTGG
ACCTCCTGGTGCCCCTGGTCCATGTTGTGGTGCTGGCGGGGTTGCTGCCATTGCT
GGTGTTGGAGCCGAAAAAGCTGGTGGTTTTGCCCCATATTATGGAGATGAACCGA
TAGATTTCAAAATCAACACCAATGAGATTATGACCTCACTCAAATCAGTCAATGG
ACAAATAGAAAGCCTCATTAGTCCTGATGGTTCCCGTAAAAACCCTGCACGGAAC
TGCAGGGACCTGAAATTCTGCCATCCTGAACTCCAGAGTGGAGAATATTGGGTTG
ATCCTAACCAAGGTTGCAAATTGGATGCTATTAAAGTCTACTGTAACATGGAAAC
TGGGGAAACGTGCATAAGTGCCAGTCCTTTGACTATCCCACAGAAGAACTGGTGG
ACAGATTCTGGTGCTGAGAAGAAACATGTTTGGTTTGGAGAATCCATGGAGGGTG
GTTTTCAGTTTAGCTATGGCAATCCTGAACTTCCCGAAGACGTCCTCGATGTCCA
GCTGGCATTCCTCCGACTTCTCTCCAGCCGGGCCTCTCAGAACATCACATATCAC
TGCAAGAATAGCATTGCATACATGGATCATGTCAGTGGGAATGTAAAGAAAGCCT
TGAAGCTGATGGGGTCAAATGAAGGTGAATTCAAGGCTGAAGGAAATAGCAAATT
CACATACACAGTTCTGGAGGATGGTTGCACAAAACACACTGGGGAATGGGGCAAA
ACAGTCTTCCAGTATCAAACACGCAAGGCCGTCAGACTACCTATTGTAGATATTG
```

Figure 5B                                                                    2

CACCCTATGATATCGGTGGTCCTGATCAAGAATTTGGTGCGGACATTGGCCCTGT
TTGCTTTTTATAAACCAAACCTGAATTC

Figure 5 C

3

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Met Met Ser Phe Val Gln Lys Gly Thr Trp Leu Leu Phe Ala
Leu Leu His Pro Thr Val Ile Leu Ala Gln Gln Glu Ala Val
Asp Gly Gly Cys Ser His Leu Gly Gln Ser Tyr Ala Asp Arg
Asp Val Trp Lys Pro Glu Pro Cys Gln Ile Cys Val Cys Asp
Ser Gly Ser Val Leu Cys Asp Asp Ile Ile Cys Asp Asp Gln
Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro Phe Gly Glu Cys
Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr Arg Pro
Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Pro Pro
Gly Ser Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile
Cys Glu Ser Cys Pro Thr Gly Gly Gln Asn Tyr Ser Pro Gln
Tyr Glu Ala Tyr Asp Val Lys Ser Gly Val Ala Gly Gly Gly
Ile Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly Pro Pro
Gly Pro Pro Gly Thr Ser Gly His Pro Gly Ala Pro Gly Ala
Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala Gly
Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg
Pro Gly Glu Arg Gly Phe Pro Gly Pro Pro Gly Met Lys Gly
Pro Ala Gly Met Pro Gly Phe Pro Gly Met Lys Gly His Arg
Gly Phe Asp Gly Arg Asn Gly Glu Lys Gly Glu Thr Gly Ala
Pro Gly Leu Lys Gly Glu Asn Gly Val Pro Gly Glu Asn Gly
Ala Pro Gly Pro Met Gly Pro Arg Gly Ala Pro Gly Glu Arg
Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly Asn
Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys
Gly Glu Val Gly Pro Ala Gly Ser Pro Gly Ser Ser Gly Ala
```

Figure 6A                                                    1

Pro Gly Gln Arg Gly Glu Pro Gly Pro Gln Gly His Ala Gly

Ala Pro Gly Pro Pro Gly Pro Pro Gly Ser Asn Gly Ser Pro

Gly Gly Lys Gly Glu Met Gly Pro Ala Gly Ile Pro Gly Ala

Pro Gly Leu Ile Gly Ala Arg Gly Pro Pro Gly Pro Pro Gly

Thr Asn Gly Val Pro Gly Gln Arg Gly Ala Ala Gly Glu Pro

Gly Lys Asn Gly Ala Lys Gly Asp Pro Gly Pro Arg Gly Glu

Arg Gly Glu Ala Gly Ser Pro Gly Ile Ala Gly Pro Lys Gly

Glu Asp Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn

Gly Leu Pro Gly Ala Ala Gly Glu Arg Gly Val Pro Gly Phe

Arg Gly Pro Ala Gly Ala Asn Gly Leu Pro Gly Glu Lys Gly

Pro Pro Gly Asp Arg Gly Gly Pro Gly Pro Ala Gly Pro Arg

Gly Val Ala Gly Glu Pro Gly Arg Asp Gly Leu Pro Gly Gly

Pro Gly Leu Arg Gly Ile Pro Gly Ser Pro Gly Gly Pro Gly

Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Thr

Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly Gln

Pro Gly Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly

Ala Pro Gly Lys Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro

Gly Pro Gln Gly Pro Ala Gly Lys Asn Gly Glu Thr Gly Pro

Gln Gly Pro Pro Gly Pro Thr Gly Pro Ser Gly Asp Lys Gly

Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu Gln Gly Leu Pro

Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu

Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro Gly

Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro Pro

Gly Ala Gly Gly Pro Pro Gly Pro Arg Gly Gly Ala Gly Pro

Pro Gly Pro Glu Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly

Pro Pro Gly Ser Ala Gly Thr Pro Gly Leu Gln Gly Met Pro

Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Lys Gly Asp

<div style="text-align:center">Figure 6B</div>

2

Lys Gly Glu Pro Gly Ser Ser Gly Val Asp Gly Ala Pro Gly

Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly Pro Pro

Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Ser Gly Ala

Pro Gly Val Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro Gly

Glu Arg Gly Glu Gln Gly Pro Pro Gly Pro Ala Gly Phe Pro

Gly Ala Pro Gly Gln Asn Gly Glu Pro Gly Ala Lys Gly Glu

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly

Ala Ala Gly Pro Ala Gly Gly Ser Gly Pro Ala Gly Pro Pro

Gly Pro Gln Gly Val Lys Gly Glu Arg Gly Ser Pro Gly Gly

Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly Pro Pro Gly

Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser Ser

Gly Ala Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly Ser

Asn Gly Ala Pro Gly Ser Pro Gly Ile Ser Gly Pro Lys Gly

Asp Ser Gly Pro Pro Gly Glu Arg Gly Ala Pro Gly Pro Gln

Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile Ala Gly Leu

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly

Ala Arg Gly Ser Pro Gly Pro Gln Gly Ile Lys Gly Glu Asn

Gly Lys Pro Gly Pro Ser Gly Gln Asn Gly Glu Arg Gly Pro

Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly

Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro

Gly Arg Asp Gly Ala Pro Gly Ala Lys Gly Asp Arg Gly Glu

Asn Gly Ser Pro Gly Ala Pro Gly Ala Pro Gly His Pro Gly

Pro Pro Gly Pro Val Gly Pro Ala Gly Lys Ser Gly Asp Arg

Gly Glu Thr Gly Pro Ala Gly Pro Ser Gly Ala Pro Gly Pro

Ala Gly Ser Arg Gly Pro Pro Gly Pro Gln Gly Pro Arg Gly

Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Met Gly Ile Lys

Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser

*Figure 6 C*                                                      3

Pro Gly Pro Ala Gly His Gln Gly Ala Val Gly Ser Pro Gly

Pro Ala Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro

Gly Lys Asp Gly Ala Ser Gly His Pro Gly Pro Ile Gly Pro

Pro Gly Pro Arg Gly Asn Arg Gly Glu Arg Gly Ser Glu Gly

Ser Pro Gly His Pro Gly Gln Pro Gly Pro Pro Gly Pro Pro

Gly Ala Pro Gly Pro Cys Cys Gly Ala Gly Gly Val Ala Ala

Ile Ala Gly Val Gly Ala Glu Lys Ala Gly Gly Phe Ala Pro

Tyr Tyr Gly Asp Glu Pro Ile Asp Phe Lys Ile Asn Thr Asn

Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu

Ser Leu Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg

Asn Cys Arg Asp Leu Lys Phe Cys His Pro Glu Leu Gln Ser

Gly Glu Tyr Trp Val Asp Pro Asn Gln Gly Cys Lys Leu Asp

Ala Ile Lys Val Tyr Cys Asn Met Glu Thr Gly Glu Thr Cys

Ile Ser Ala Ser Pro Leu Thr Ile Pro Gln Lys Asn Trp Trp

Thr Asp Ser Gly Ala Glu Lys Lys His Val Trp Phe Gly Glu

Ser Met Glu Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu

Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg

Leu Leu Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys

Lys Asn Ser Ile Ala Tyr Met Asp His Val Ser Gly Asn Val

Lys Lys Ala Leu Lys Leu Met Gly Ser Asn Glu Gly Glu Phe

Lys Ala Glu Gly Asn Ser Lys Phe Thr Tyr Thr Val Leu Glu

Asp Gly Cys Thr Lys His Thr Gly Glu Trp Gly Lys Thr Val

Phe Gln Tyr Gln Thr Arg Lys Ala Val Arg Leu Pro Ile Val

Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe

Gly Ala Asp Ile Gly Pro Val Cys Phe Leu

Figure 6D                                                    4

GAATTCAGGGACATGTTCAGCTTTGTGGACCTCCGGCTCCTGCTCCTCTTAGCGG
CCACCGCCCTCCTGACGCACGGCCAAGAGGAGGGCCAAGAAGAAGGCCAACAAGG
CCAAGAAGAAGACATCCCACCAGTCACCTGCGTACAGAACGGCCTCAGGTACCAT
GACCGAGACGTGTGGAAACCCGTGCCCTGCCAGATCTGTGTCTGCGACAACGGCA
ATGTGTTGTGCGATGACGTGATCTGCGACGAAATCAAGAACTGTCCCAGCGCCAG
AGTCCCTGCGGGCGAGTGCTGCCCCGTCTGCCCCGAAGGCGAGGTGTCACCCACC
GACCAGGAAACCACGGGAGTCGAGGGACCCAAGGGAGACACTGGCCCCCGAGGCC
CCAGGGGACCCTCTGGCCCCCCTGGCCGAGACGGCATCCCTGGACAACCTGGACT
TCCTGGACCCCCGGACCTCCTGGACCCCCGGACCCCCTGGCCTCGGAGGAAAC
TTTGCTCCCCAGTTGTCTTATGGCTATGATGAGAAGTCAGCAGGAATTTCCGTGC
CCGGCCCCATGGGTCCTTCTGGTCCTCGTGGTCTCTCTGGCCCCCCTGGCGCACC
TGGTCCCCAAGGTTTCCAAGGCCCCCCTGGTGAGCCTGGCGAGCCTGGCGCCTCC
GGTCCCATGGGTCCCCGTGGTCCTCCTGGCCCCCCTGGCAAGAACGGAGATGATG
GTGAAGCTGGAAAGCCTGGTCGCCCTGGTGAGCGTGGGCCTCCTGGACCTCAGGG
TGCTCGGGGATTGCCCGGAACAGCTGGCCTCCCTGGAATGAAGGGACACAGAGGT
TTCAGTGGTTTGGATGGTGCCAAGGGAGATGCTGGTCCTGCTGGTCCCAAGGGTG
AGCCTGGTAGCCCTGGTGAAAATGGAGCTCCTGGTCAGATGGGCCCCCGTGGTCT
GCCTGGTGAGCGAGGTCGCCCTGGACCCCCTGGCCCTGCTGGTGCTCGTGGAAAT
GATGGTGCTACTGGTGCTGCTGGACCCCCTGGTCCCACTGGCCCCGCTGGTCCTC
CTGGCTTCCCTGGTGCTGTTGGTGCTAAGGGTGAAGCTGGTCCCCAAGGAGCCCG
AGGCTCTGAAGGTCCCCAGGGTGTGCGTGGTGAGCCTGGCCCCCCTGGCCCTGCT
GGTGCTGCTGGCCCTGCTGGAAACCCTGGTGCTGATGGACAGCCTGGTGGCAAAG
GTGCCAACGGCGCTCCTGGTATTGCTGGTGCTCCTGGCTTCCCTGGTGCCCGAGG
CCCCTCTGGACCCCAGGGTCCCAGCGGCCCCCCTGGTCCCAAGGGTAACAGCGGT
GAACCTGGTGCTCCCGGCAGCAAAGGAGACACTGGCGCCAAGGGAGAGCCCGGTC
CCACTGGTGTTCAAGGACCCCCTGGCCCTGCTGGAGAAGAAGGAAAGCGAGGAGC
CCGAGGTGAACCTGGACCTGCTGGCCTGCCTGGACCCCCTGGCGAGCGTGGTGGA
CCTGGTAGCCGTGGTTTCCCTGGCGCCGATGGTGTTGCTGGTCCCAAGGGTCCCG
CTGGTGAACGTGGTTCTCCTGGCCCTGCTGGTCCCAAAGGTTCTCCTGGTGAAGC
TGGTCGCCCCGGTGAAGCTGGTCTGCCTGGTGCCAAGGGTCTGACTGGAAGCCCT
GGCAGCCCTGGTCCTGATGGCAAAACTGGCCCCCCTGGTCCCGCCGGTCAAGATG
GTCGCCCTGGACCCCCAGGCCCTCCTGGTGCCCGTGGTCAGGCTGGTGTGATGGG
TTTCCCTGGACCTAAAGGTGCTGCTGGAGAGCCTGGCAAAGCTGGAGAGCGAGGT
GTTCCCGGACCCCCTGGCGCAGTTGGTCCTGCTGGCAAAGATGGAGAAGCTGGAG
CTCAGGGACCCCCCGGACCTGCTGGCCCCGCTGGTGAGAGAGGAGAACAAGGCCC
CGCTGGCTCCCCTGGATTCCAGGGTCTCCCTGGCCCTGCTGGTCCTCCTGGTGAA
GCAGGCAAACCCGGTGAACAGGGTGTTCCTGGAGATCTCGGTGCCCCCGGCCCCT
CTGGAGCAAGAGGCGAGAGAGGTTTCCCCGGCGAGCGTGGTGTGCAAGGTCCCCC
CGGTCCTGCAGGTCCCCGTGGAGCCAACGGTGCCCCTGGCAATGATGGTGCTAAG

Figure 7A

1

GGTGATGCTGGTGCCCCTGGAGCCCCTGGTAGCCAGGGCGCCCCTGGCCTTCAGG
GAATGCCTGGCGAACGAGGTGCAGCTGGTCTCCCAGGTCCTAAGGGTGACAGAGG
AGATGCTGGTCCCAAAGGTGCTGATGGTGCTCCTGGCAAAGATGGCGTCCGTGGT
CTGACTGGCCCCATTGGTCCTCCCGGCCCCGCTGGTGCCCCTGGTGACAAGGGTG
AAACTGGTCCTAGCGGTCCTGCTGGTCCCACTGGAGCTCGTGGTGCCCCCGGTGA
CCGTGGTGAGCCTGGTCCCCCCGGCCCTGCTGGCTTCGCTGGCCCCCCTGGTGCT
GATGGCCAACCTGGTGCTAAAGGCGAACCTGGTGATGCTGGTGCTAAAGGCGATG
CTGGTCCCCCCGGCCCTGCTGGACCCACTGGCCCCCCTGGCCCCATTGGTAGCGT
TGGTGCTCCCGGACCCAAAGGTGCTCGTGGCAGCGCTGGTCCTCCTGGTGCTACT
GGTTTCCCTGGTGCTGCTGGCCGAGTCGGTCCCCCCGGCCCCTCTGGAAATGCTG
GACCCCCTGGCCCTCCTGGTCCTGCTGGCAAAGAAGGCAGCAAAGGTCCCCGTGG
TGAGACTGGCCCCGCTGGGCGTCCCGGTGAAGCCGGTCCCCCTGGCCCCCCTGGC
CCCGCTGGTGAGAAAGGATCCCCTGGTGCTGACGGACCTGCTGGTGCTCCCGGTA
CTCCTGGACCTCAGGGTATTGCTGGACAGCGTGGTGTGGTCGGCCTGCCCGGTCA
ACGAGGAGAAAGAGGCTTCCCTGGTCTTCCCGGCCCATCTGGTGAACCCGGCAAA
CAAGGTCCTTCTGGACCAAGCGGCGAACGTGGCCCCCCTGGTCCCATGGGCCCCC
CTGGATTGGCTGGACCCCCTGGCGAGTCTGGACGTGAGGGAGCCCCTGGCGCTGA
AGGATCCCCTGGACGAGATGGTGCTCCTGGCCCCAAGGGTGACCGTGGTGAGAGC
GGCCCTGCTGGACCCCCTGGTGCTCCTGGTGCTCCTGGTGCCCCCGGCCCCGTTG
GCCCTGCTGGCAAGAGCGGCGATCGTGGTGAGACTGGTCCTGCTGGTCCTGCTGG
TCCCGTTGGCCCCGTTGGTGCCCGTGGCCCTGCTGGACCCCAAGGCCCCCGTGGT
GACAAGGGTGAGACAGGCGAACAGGGCGACAGAGGCATTAAGGGTCACCGTGGCT
TCTCTGGTCTCCAGGGTCCCCCTGGCCCTCCCGGCTCTCCTGGTGAGCAAGGTCC
CTCCGGAGCTTCTGGTCCCGCTGGTCCCCGAGGTCCCCCTGGCTCTGCTGGTGCT
CCTGGCAAAGATGGACTCAACGGTCTCCCCGGCCCCATCGGTCCCCCTGGGCCTC
GTGGTCGCACTGGTGATGCTGGCCCTGTTGGTCCTCCCGGCCCTCCTGGACCCCC
CGGTCCCCCTGGTCCTCCCAGCGGCGGTTTCGACTTCAGCTTCTTGCCCCAGCCA
CCTCAAGAGAAGGCTCACGATGGTGGCCGCTACTACCGGGCCGATGATGCCAATG
TGGTCCGCGACCGTGACCTCGAGGTGGACACCACCCTCAAGAGCCTGAGCCAGCA
GATCGAGAACATCCGGAGCCCCGAAGGCAGCCGCAAGAACCCCGCCCGCACCTGC
CGCGACCTCAAGATGTGCCACTCCGACTGGAAGAGCGGAGAATACTGGATTGACC
CCAACCAAGGCTGCAACCTGGACGCCATCAAAGTCTTCTGCAACATGGAGACAGG
CGAGACCTGCGTGTACCCCACTCAGCCCAGCGTGCCCCAGAAGAACTGGTACATC
AGCAAGAACCCCAAGGACAAGAGGCACGTCTGGTACGGCGAGAGCATGACCGACG
GATTCCAGTTCGAGTACGGCGGCGAGGGCTCCGATCCTGCTGACGTGGCCATCCA
GCTGACCTTCCTGCGCCTGATGTCCACTGAGGCTTCCCAGAACATCACCTACCAC
TGCAAGAACAGCGTGGCCTACATGGACCAGCAGACTGGCAACCTCAAGAAGGCCC
TGCTCCTCCAGGGCTCCAACGAGATCGAGATCCGGGCCGAGGGCAACAGCCGCTT
CACCTACAGCGTGATCTACGACGGCTGCACGAGTCACACCGGAGCCTGGGGCAAG
ACAGTGATCGAATACAAAACCACCAAGACCTCCCGCCTGCCCATCATCGATGTGG

Figure 7B

2

CCCCCTTGGACGTTGGCGCCCCCGACCAAGAATTCGGCATCGACCTTAGCCCTGT
CTGCTTCCTGTAAACTCCTGAATTC

Figure 7C

3

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Leu Ala
Ala Thr Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Glu
Glu Gly Gln Gln Gly Gln Glu Glu Asp Ile Pro Pro Val Thr
Cys Val Gln Asn Gly Leu Arg Tyr His Asp Arg Asp Val Trp
Lys Pro Val Pro Cys Gln Ile Cys Val Cys Asp Asn Gly Asn
Val Leu Cys Asp Asp Val Ile Cys Asp Glu Ile Lys Asn Cys
Pro Ser Ala Arg Val Pro Ala Gly Glu Cys Cys Pro Val Cys
Pro Glu Gly Glu Val Ser Pro Thr Asp Gln Glu Thr Thr Gly
Val Glu Gly Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg
Gly Pro Ser Gly Pro Pro Gly Arg Asp Gly Ile Pro Gly Gln
Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
Pro Pro Gly Leu Gly Gly Asn Phe Ala Pro Gln Leu Ser Tyr
Gly Tyr Asp Glu Lys Ser Ala Gly Ile Ser Val Pro Gly Pro
Met Gly Pro Ser Gly Pro Arg Gly Leu Ser Gly Pro Pro Gly
Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro
Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro
Pro Gly Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly
Lys Pro Gly Arg Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln
Gly Ala Arg Gly Leu Pro Gly Thr Ala Gly Leu Pro Gly Met
Lys Gly His Arg Gly Phe Ser Gly Leu Asp Gly Ala Lys Gly
Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu Pro Gly Ser Pro
Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg Gly Leu
Pro Gly Glu Arg Gly Arg Pro Gly Pro Pro Gly Pro Ala Gly
Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro
Gly Pro Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala
Val Gly Ala Lys Gly Glu Ala Gly Pro Gln Gly Ala Arg Gly

1

Figure 8A

```
Ser Glu Gly Pro Gln Gly Val Arg Gly Glu Pro Gly Pro Pro
Gly Pro Ala Gly Ala Ala Gly Pro Ala Gly Asn Pro Gly Ala
Asp Gly Gln Pro Gly Gly Lys Gly Ala Asn Gly Ala Pro Gly
Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly Pro Ser
Gly Pro Gln Gly Pro Ser Gly Pro Pro Gly Pro Lys Gly Asn
Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly
Ala Lys Gly Glu Pro Gly Pro Thr Gly Val Gln Gly Pro Pro
Gly Pro Ala Gly Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu
Pro Gly Pro Ala Gly Leu Pro Gly Pro Pro Gly Glu Arg Gly
Gly Pro Gly Ser Arg Gly Phe Pro Gly Ala Asp Gly Val Ala
Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly Ser Pro Gly Pro
Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg Pro Gly
Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro
Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro
Ala Gly Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly
Ala Arg Gly Gln Ala Gly Val Met Gly Phe Pro Gly Pro Lys
Gly Ala Ala Gly Glu Pro Gly Lys Ala Gly Glu Arg Gly Val
Pro Gly Pro Pro Gly Ala Val Gly Pro Ala Gly Lys Asp Gly
Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro Ala Gly Pro Ala
Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro Gly Phe
Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly
Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro
Gly Pro Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu
Arg Gly Val Gln Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly
Ala Asn Gly Ala Pro Gly Asn Asp Gly Ala Lys Gly Asp Ala
Gly Ala Pro Gly Ala Pro Gly Ser Gln Gly Ala Pro Gly Leu
Gln Gly Met Pro Gly Glu Arg Gly Ala Ala Gly Leu Pro Gly
```

Figure 8B

2

Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly Ala Asp
Gly Ala Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro
Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly
Glu Thr Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg
Gly Ala Pro Gly Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro
Ala Gly Phe Ala Gly Pro Pro Gly Ala Asp Gly Gln Pro Gly
Ala Lys Gly Gly Pro Thr Gly Pro Pro Gly Pro Ile Gly Ser
Val Gly Ala Pro Gly Pro Lys Gly Ala Arg Gly Ser Ala Gly
Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala Gly Arg Val
Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly Pro
Pro Gly Pro Ala Gly Lys Glu Gly Ser Lys Gly Pro Arg Gly
Glu Thr Gly Pro Ala Gly Arg Pro Gly Glu Ala Gly Pro Pro
Gly Pro Pro Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala
Asp Gly Pro Ala Gly Ala Pro Gly Thr Pro Gly Pro Gln Gly
Ile Ala Gly Gln Arg Gly Val Val Gly Leu Pro Gly Gln Arg
Gly Glu Arg Gly Phe Pro Gly Leu Pro Gly Pro Ser Gly Glu
Pro Gly Lys Gln Gly Pro Ser Gly Pro Ser Gly Glu Arg Gly
Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro Pro
Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser
Pro Gly Arg Asp Gly Ala Pro Gly Pro Lys Gly Asp Arg Gly
Glu Ser Gly Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro
Gly Ala Pro Gly Pro Val Gly Pro Ala Gly Lys Ser Gly Asp
Arg Gly Glu Thr Gly Pro Ala Gly Pro Ala Gly Pro Val Gly
Pro Val Gly Ala Arg Gly Pro Ala Gly Pro Gln Gly Pro Arg
Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp Arg Gly Ile
Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro Gly
Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser

<div style="text-align: right">3</div>

Figure 8C

Gly Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala

Pro Gly Lys Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly

Pro Pro Gly Pro Arg Gly Arg Thr Gly Asp Ala Gly Pro Val

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro

Pro Ser Gly Gly Phe Asp Phe Ser Phe Leu Pro Gln Pro Pro

Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr Arg Ala Asp

Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp Thr

Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser

Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp

Leu Lys Met Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp

Ile Asp Pro Asn Gln Gly Cys Asn Leu Asp Ala Ile Lys Val

Phe Cys Asn Met Glu Thr Gly Glu Thr Cys Val Tyr Pro Thr

Gln Pro Ser Val Pro Gln Lys Asn Trp Tyr Ile Ser Lys Asn

Pro Lys Asp Lys Arg His Val Trp Tyr Gly Glu Ser Met Thr

Asp Gly Phe Gln Phe Glu Tyr Gly Gly Glu Gly Ser Asp Pro

Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser

Thr Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser

Val Ala Tyr Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala

Leu Leu Leu Gln Gly Ser Asn Glu Ile Glu Ile Arg Ala Glu

Gly Asn Ser Arg Phe Thr Tyr Ser Val Ile Tyr Asp Gly Cys

Thr Ser His Thr Gly Ala Trp Gly Lys Thr Val Ile Glu Tyr

Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile Ile Asp Val Ala

Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Ile Asp

Leu Ser Pro Val Cys Phe Leu

Figure 8D

4

GAATTCAGGGACATGCTCAGCTTTGTGGATACGCGGACTTTGTTGCTGCTTGCAG
TAACTTCGTGCCTAGCAACATGCCAATCTTTACAAGAGGCAACTGCAAGAAAGGG
CCCAACTGGAGATAGAGGACCACGCGGAGAAAGGGGTCCACCAGGCCCACCAGGC
AGAGATGGTGATGATGGTATCCCAGGCCCTCCTGGTCCACCTGGTCCTCCTGGCC
CCCCTGGTCTTGGCGGGAACTTTGCTGCTCAGTATGATGGAAAAGGAGTTGGAGC
TGGCCCTGGACCAATGGGTTTGATGGGACCTAGGGGCCCTCCTGGGGCAGTTGGA
GCCCCTGGCCCTCAAGGTTTCCAAGGACCTGCTGGTGAGCCTGGCGAACCTGGTC
AGACTGGTCCTGCTGGTGCTCGTGGTCCACCTGGCCCTCCTGGCAAGGCTGGTGA
GGATGGTCACCCTGGAAAACCCGGACGACCTGGTGAGAGAGGAGTTGTTGGACCA
CAGGGTGCTCGTGGTTTCCCTGGAACTCCTGGACTTCCTGGCTTCAAGGGCATTA
GGGGTCACAACGGTCTGGATGGATTGAAGGGACAGCCCGGTGCTCCAGGTGTGAA
GGGCGAACCTGGTGCCCCCGGCGAAAATGGAACTCCAGGTCAAACAGGAGCTCGC
GGGCTTCCTGGTGAGAGAGGACGTGTCGGTGCTCCTGGCCCAGCTGGTGCCCGTG
GAAATGATGGAAGTGTGGGTCCTGTGGGTCCTGCTGGTCCCATTGGGTCTGCTGG
CCCTCCAGGCTTCCCAGGTGCTCCTGGCCCCAAGGGTGAACTTGGACCTGTTGGT
AACCCTGGTCCTGCAGGTCCTGCGGGTCCCCGTGGTGAAGTGGGTCTTCCAGGTG
TTTCTGGCCCTGTTGGACCTCCTGGCAACCCTGGAGCCAACGGCCTTCCTGGTGC
TAAAGGTGCTGCTGGCCTGCTTGGTGTTGCTGGGGCTCCTGGCCTCCCTGGGCCT
CGAGGTATTCCTGGCCCTGCTGGTGCTGCTGGTGCTACTGGTGCCAGAGGTCTTG
TTGGTGAGCCTGGTCCAGCTGGTTCCAAAGGAGAGAGCGGCAACAAGGGCGAGCC
TGGTGCTGCTGGGCCCCAAGGTCCTCCTGGTCCCAGTGGTGAAGAAGGAAAGAGA
GGCCCCAATGGAGAAGTTGGATCTGCTGGCCCCCCAGGACCTCCTGGGCTGAGGG
GAAATCCTGGTTCTCGTGGTCTCCCTGGAGCTGATGGCAGAGCTGGTGTCATGGG
CCCTCCTGGTAGTCGTGGTCCAACTGGCCCTGCTGGTGTTCGAGGTCCCAATGGA
GATTCTGGTCGCCCTGGAGAGCCTGGCCTTATGGGACCCCGAGGTTTCCCTGGAT
CCCCTGGAAATGTTGGTCCAGCTGGTAAAGAAGGTCCTGCGGGCCTCCCTGGTAT
TGATGGCAGGCCTGGACCAATTGGCCCAGCTGGAGCAAGAGGAGAGCCTGGCAAC
ATTGGATTCCCTGGACCCAAAGGCCCCACTGGTGATCCTGGCAAAAATGGTGAAA
AAGGTCATGCTGGTCTGGCTGGTGCTCGGGGTGCCCCAGGTCCTGATGGAAACAA
TGGTGCTCAGGGACCTCCTGGACCACAGGGTGTTCAAGGTGGAAAAGGTGAACAA
GGTCCCGCTGGTCCTCCAGGCTTCCAGGGTCTCCCTGGCCCCGCAGGTACAGCTG
GTGAAGTTGGCAAACCAGGAGAAAGGGGTATCCCTGGTGAATTTGGTCTCCCTGG
TCCTGCTGGTCCAAGAGGGGAGCGTGGTCCCCCAGGTGAAAGTGGTGCTGCTGGT
CCTGCTGGTCCTATTGGAAGCCGAGGTCCTTCTGGACCCCCGGGGCCTGATGGCA
ACAAGGGCGAACCTGGTGTGCTTGGTGCTCCAGGCACTGCTGGTCCATCTGGTCC
TAGTGGACTCCCAGGAGAGAGGGGTGCTGCTGGCATACCTGGAGGCAAGGGAGAA
AAGGGTGAAACTGGTCTCAGAGGTGACGTTGGTAGCCCTGGCAGAGATGGTGCTC
GTGGTGCTCCTGGTGCTGTAGGTGCCCCTGGTCCTGCTGGAGCCAATGGGGACCG
GGGTGAAGCTGGCCCTGCTGGCCCTGCTGGCCCTGCTGGTCCTCGTGGTAGTCCT

Figure 9 A                                                    1

GGTGAACGTGGTGAGGTTGGTCCTGCTGGCCCCAATGGATTTGCTGGTCCTGCTG
GTGCTGCCGGTCAACCTGGTGCTAAAGGAGAGAGAGGAACCAAAGGGCCCAAAGG
TGAAAATGGTCCTGTTGGTCCCACAGGCCCTGTTGGAGCTGCTGGCCCAGCTGGT
CCAAATGGTCCTCCTGGTCCTGCTGGCAGTCGTGGTGATGGCGGCCCCCCTGGTG
CTACTGGTTTCCCTGGTGCTGCTGGACGGATTGGTCCTCCTGGACCTTCTGGTAT
CTCTGGGCCCCCTGGACCCCCTGGTCCTGCTGGGAAAGAAGGACTTCGTGGGCCT
CGTGGTGACCAAGGTCCAGTTGGTCGAACTGGAGAAACAGGTGCATCTGGCCCCC
CTGGCTTTGCTGGTGAGAAAGGTCCCTCTGGAGAGCCTGGTACTGCTGGACCTCC
TGGTACCCCAGGTCCTCAAGGTATTCTTGGTGCTCCTGGTTTTCTGGGTCTCCCT
GGCTCTAGAGGTGAACGTGGTCTACCAGGTGTTGCTGGATCAGTGGGTGAACCTG
GCCCCCTCGGCATTGCAGGCCCACCTGGGGCCCGTGGTCCCCCTGGTGCTGTGGG
TAATCCTGGTGTCAATGGTGCTCCTGGTGAAGCTGGTCGTGATGGCAACCCTGGA
AGCGATGGTCCCCCAGGCCGAGATGGTCAAGCTGGACACAAGGGCGAGCGTGGTT
ACCCTGGTAATCCTGGTCCTGCTGGTGCTGCAGGAGCACCTGGTCCTCAAGGTGC
TGTGGGTCCCGCTGGCAAACATGGAAACCGTGGTGAACCTGGTCCTGCTGGTTCT
GTTGGTCCTGCTGGTGCTGTTGGTCCAAGAGGTCCTAGTGGCCCACAAGGTATTC
GAGGTGAGAAGGGAGAGCCTGGTGATAAGGGGCCCAGAGGTCTTCCTGGCTTGAA
GGGACACAACGGATTGCAAGGTCTTCCTGGTCTTGCTGGTCATCATGGTGATCAA
GGTGCTCCTGGCCCTGTGGGTCCTGCTGGTCCTAGGGGTCCAGCTGGTCCTTCTG
GCCCTGCTGGCAAAGATGGTCGCACTGGACAACCTGGTGCAGTTGGACCTGCTGG
CATTCGTGGCTCTCAAGGAAGCCAAGGTCCTGCTGGTCCTCCTGGTCCTCCTGGC
CCTCCTGGACCACCTGGCCCAAGTGGTGGTGGTTATGATTTGGATATGAAGGAG
ACTTCTACAGGGCTGACCAGCCTCGCTCACCACCTTCTCTCAGACCCAAGGATTA
TGAAGTTGATGCTACTCTGAAATCTCTCAACAACCAGATTGAGACTCTACTTACT
CCAGAAGGCTCTAGGAAGAACCCAGCTCGCACATGCCGTGACTTGAGACTCAGCC
ACCCAGAATGGAGTAGTGGTTACTACTGGATTGACCCTAACCAAGGATGTACTAT
GGATGCTATCAAAGTATACTGTGATTTCTCTACTGGTGAAACCTGCATTCGGGCT
CAACCTGAAAACATCCCAGCCAAAAACTGGTACAGAAACTCCAAGGTCAAGAAGC
ACGTCTGGTTAGGAGAAACTATCAATGGTGGTACCCAGTTTGAATATAATATGGA
AGGAGTTACCACCAAGGAAATGGCTACACAACTTGCCTTCATGCGCCTGCTGGCC
AACCATGCCTCCCAAAACATCACCTACCATTGCAAGAACAGCATTGCATACATGG
ATGAAGAGACTGGCAACCTGAAAAAGGCTGTCATTCTGCAAGGATCCAATGATGT
TGAACTTGTTGCCGAGGGCAACAGCAGATTCACCTACACTGTTCTTGTAGATGGC
TGTTCTAAAAAAACAAATGAATGGAGAAAAACAATCATTGAATATAAAACAAATA
AGCCATCTCGCCTGCCTATCCTTGATATTGCACCTTTGGACATCGGTGATGCTGA
CCAAGAAGTCAGTGTGGACGTTGGCCCAGTCTGTTTCAAATAAATGAACTCAACC
TAAATTAAAGAAAAAGGAAATCTGAAAAATTTCTCTCTTTGCCATTTCTTTTTCT
TCTTTTTAACTGAAAGCTGAATCATTCCATTTCTTCTGCACATCTACTTGCTTAA
ATTGTGGGCAAAAGAGAAGGAGAAGGATTGATCAGAGCATCGTGCAATACAATTA
ATTCGTTCCCTGTCCCTCTTCCCCTCCCCAAAAGATTTGGAATTTTTTTCAACAT

<p style="text-align: center;">Figure 9B</p>

2

TCTAACACCTGTTGTGGAAAATGTCAACCTTTGTAAGAAAACCAAAAATAAAAAT
TGAAAAATAAAATAAAAACCATGAACATTTGCACCACTTGTGGCTTTTGAATATC
TTCCACAGAGGGAAGTTTAAAACCCAAACTTCCACCTGAATTC

Figure 9C

3

Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala
Val Thr Ser Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Ala
Thr Ala Arg Lys Gly Pro Thr Gly Asp Arg Gly Pro Arg Gly
Glu Arg Gly Pro Pro Gly Pro Pro Gly Arg Asp Gly Asp Asp
Gly Ile Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro
Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln Tyr Asp Gly Lys
Gly Val Gly Ala Gly Pro Gly Pro Met Gly Leu Met Gly Pro
Arg Gly Pro Pro Gly Ala Val Gly Ala Pro Gly Pro Gln Gly
Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr
Gly Pro Ala Gly Ala Arg Gly Pro Pro Gly Pro Pro Gly Lys
Ala Gly Glu Asp Gly His Pro Gly Lys Pro Gly Arg Pro Gly
Glu Arg Gly Val Val Gly Pro Gln Gly Ala Arg Gly Phe Pro
Gly Thr Pro Gly Leu Pro Gly Phe Lys Gly Ile Arg Gly His
Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro Gly Ala Pro Gly
Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly Thr Pro
Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Asn Asp Gly
Ser Val Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala
Gly Pro Pro Gly Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu
Leu Gly Pro Val Gly Asn Pro Gly Pro Ala Gly Pro Ala Gly
Pro Arg Gly Glu Val Gly Leu Pro Gly Val Ser Gly Pro Val
Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly Leu Pro Gly Ala
Lys Gly Ala Ala Gly Leu Leu Gly Val Ala Gly Ala Pro Gly
Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Ala Gly Ala Ala
Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro
Ala Gly Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly
Ala Ala Gly Pro Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu
Gly Lys Arg Gly Pro Asn Gly Glu Val Gly Ser Ala Gly Pro
Pro Gly Pro Pro Gly Leu Arg Gly Asn Pro Gly Ser Arg Gly
Leu Pro Gly Ala Asp Gly Arg Ala Gly Val Met Gly Pro Pro
Gly Ser Arg Gly Pro Thr Gly Pro Ala Gly Val Arg Gly Pro
Asn Gly Asp Ser Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
Pro Arg Gly Phe Pro Gly Ser Pro Gly Asn Val Gly Pro Ala
Gly Lys Glu Gly Pro Ala Gly Leu Pro Gly Ile Asp Gly Arg
Pro Gly Pro Ile Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly
Asn Ile Gly Phe Pro Gly Pro Lys Gly Pro Thr Gly Asp Pro
Gly Lys Asn Gly Glu Lys Gly His Ala Gly Leu Ala Gly Ala
Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn Gly Ala Gln Gly
Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly Glu Gln

Figure 10A

1

Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
Ala Gly Thr Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly
Ile Pro Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg
Gly Glu Arg Gly Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro
Ala Gly Pro Ile Gly Ser Arg Gly Pro Ser Gly Pro Pro Gly
Pro Asp Gly Asn Lys Gly Glu Pro Gly Val Leu Gly Ala Pro
Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly Leu Pro Gly Glu
Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu Lys Gly
Glu Thr Gly Leu Arg Gly Asp Val Gly Ser Pro Gly Arg Asp
Gly Ala Arg Gly Ala Pro Gly Ala Val Gly Ala Pro Gly Pro
Ala Gly Ala Asn Gly Asp Arg Gly Glu Ala Gly Pro Ala Gly
Pro Ala Gly Pro Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
Gly Glu Val Gly Pro Ala Gly Pro Asn Gly Phe Ala Gly Pro
Ala Gly Ala Ala Gly Gln Pro Gly Ala Lys Gly Glu Arg Gly
Thr Lys Gly Pro Lys Gly Glu Asn Gly Pro Val Gly Pro Thr
Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn Gly Pro
Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly
Ala Thr Gly Phe Pro Gly Ala Ala Gly Arg Ile Gly Pro Pro
Gly Pro Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro
Ala Gly Lys Glu Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly
Pro Val Gly Arg Thr Gly Glu Thr Gly Ala Ser Gly Pro Pro
Gly Phe Ala Gly Glu Lys Gly Pro Ser Gly Glu Pro Gly Thr
Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln Gly Ile Leu Gly
Ala Pro Gly Phe Leu Gly Leu Pro Gly Ser Arg Gly Glu Arg
Gly Leu Pro Gly Val Ala Gly Ser Val Gly Glu Pro Gly Pro
Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly
Ala Val Gly Asn Pro Gly Val Asn Gly Ala Pro Gly Glu Ala
Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Pro Pro Gly Arg
Asp Gly Gln Ala Gly His Lys Gly Glu Arg Gly Tyr Pro Gly
Asn Pro Gly Pro Ala Gly Ala Ala Gly Ala Pro Gly Pro Gln
Gly Ala Val Gly Pro Ala Gly Lys His Gly Asn Arg Gly Glu
Pro Gly Pro Ala Gly Ser Val Gly Pro Ala Gly Ala Val Gly
Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Glu Lys
Gly Glu Pro Gly Asp Lys Gly Pro Arg Gly Leu Pro Gly Leu
Lys Gly His Asn Gly Leu Gln Gly Leu Pro Gly Leu Ala Gly
His His Gly Asp Gln Gly Ala Pro Gly Pro Val Gly Pro Ala
Gly Pro Arg Gly Pro Ala Gly Pro Ser Gly Pro Ala Gly Lys
Asp Gly Arg Thr Gly Gln Pro Gly Ala Val Gly Pro Ala Gly
Ile Arg Gly Ser Gln Gly Ser Gln Gly Pro Ala Gly Pro Pro
Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Ser Gly Gly

Figure 10β                                                        2

```
Gly Tyr Asp Phe Gly Tyr Glu Gly Asp Phe Tyr Arg Ala Asp
Gln Pro Arg Ser Pro Pro Ser Leu Arg Pro Lys Asp Tyr Glu
Val Asp Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr
Leu Leu Thr Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr
Cys Arg Asp Leu Arg Leu Ser His Pro Glu Trp Ser Ser Gly
Tyr Tyr Trp Ile Asp Pro Asn Gln Gly Cys Thr Met Asp Ala
Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly Glu Thr Cys Ile
Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp Tyr Arg
Asn Ser Lys Val Lys Lys His Val Trp Leu Gly Glu Thr Ile
Asn Gly Gly Thr Gln Phe Glu Tyr Asn Met Glu Gly Val Thr
Thr Lys Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu
Ala Asn His Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn
Ser Ile Ala Tyr Met Asp Glu Glu Thr Gly Asn Leu Lys Lys
Ala Val Ile Leu Gln Gly Ser Asn Asp Val Glu Leu Val Ala
Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val Leu Val Asp Gly
Cys Ser Lys Lys Thr Asn Glu Trp Arg Lys Thr Ile Ile Glu
Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Ile Leu Asp Ile
Ala Pro Leu Asp Ile Gly Asp Ala Asp Gln Glu Val Ser Val
Asp Val Gly Pro Val Cys Phe Lys
```

Figure 10 C

3

```
GAATTCAGGGACATGATGAGCTTTGTGCAAAAGGGGACCTGGTTACTTTTTGCTC
TACTTCATCCCACTGTTATTTTGGCACAACAACAGGAAGCTATTGAAGGAGGATG
CTCCCATCTTGGTCAGTCCTATGCGGATAGAGATGTCTGGAAGCCAGAACCATGT
CAAATATGCGTCTGTGACTCAGGATCTGTTCTCTGCGATGATATAATATGTGATG
ATCAAGAATTAGACTGTCCCAACCCTGAGATCCCATTTGGAGAATGTTGTGCAGT
TTGTCCACAACCTCCAACAGCTCCCACCCGCCCTCCCAATGGTCATGGACCTCAA
GGCCCCAAGGGAGATCCAGGCCCTCCTGGTATTCCTGGGAGAAATGGAGACCCTG
GTCTTCCAGGACAACCAGGTTCCCCTGGTTCTCCTGGGCCTCCTGGAATCTGTGA
ATCATGCCCTACTGGTGGCCAGAACTATTCTCCCCAGTATGAGTCATATGATGTC
AAGGCTGGAGTAGCAGGAGGAGGAATCGGAGGCTATCCTGGGCCAGCAGGTCCCC
CTGGCCCACCTGGTCCCCCTGGTGTATCTGGTCATCCTGGTGCCCCTGGTTCTCC
AGGATACCAAGGGCCCCCTGGTGAACCTGGGCAAGCTGGTCCTGCAGGTCCTCCA
GGGCCTCCTGGTGCTATAGGTCCATCTGGTCCTGCCGGAAAAGATGGGGAGTCAG
GAAGACCCGGACGACCTGGAGAACGAGGATTGCCTGGCCCTCCAGGTCTCAAAGG
TCCAGCTGGCATGCCTGGATTCCCTGGTATGAAAGGGCATAGAGGCTTTGATGGA
CGAAATGGAGAAAAAGGTGATACAGGTGCTCCTGGGCTGAAGGGTGAAAATGGCC
TTCCAGGTGAAAATGGAGCTCCTGGACCCATGGGTCCAAGAGGGGCTCCTGGTGA
GCGAGGACGGCCAGGACTTCCTGGAGCTGCAGGGGCTCGAGGTAATGATGGTGCC
CGAGGAAGTGATGGACAACCAGGTCCCCCTGGTCCCCCTGGAACTGCAGGATTCC
CTGGTTCCCCTGGTGCTAAGGGTGAAGTTGGACCCGCGGGATCTCCTGGTCCAAG
TGGATCCCCTGGACAAAGAGGAGAACCTGGACCTCAGGGACATGCCGGTGCTGCA
GGTCCTCCTGGCCCTCCTGGGAGTAATGGTAGTCCTGGTGGCAAAGGTGAAATGG
GTCCTGCTGGCATCCCTGGAGCTCCTGGATTGATGGGAGCCCGTGGTCCTCCAGG
ACCACCTGGTACCAATGGTGCTCCTGGGCAACGAGGTGCAGCAGGTGAACCTGGT
AAAAATGGGGCCAAAGGAGAGCCAGGACCACGTGGTGAACGTGGGGAAGCTGGTT
CTCCGGGTATTCCAGGACCCAAGGGTGAAGATGGCAAAGATGGTTCTCCTGGAGA
ACCTGGTGCAAATGGACTTCCAGGAGCTGCAGGAGAAAGGGGTATGCCTGGATTC
CGAGGAGCTCCTGGAGCAAATGGCCTTCCAGGAGAAAAGGGTCCCGCTGGCGAGC
GCGGTGGTCCAGGCCCCGCAGGCCCCAGAGGAGTTGCCGGAGAACCTGGCCGAGA
TGGTGTTCCTGGAGGTCCAGGATTGAGGGGCATGCCCGGTAGCCCCGGAGGACCA
GGCAGTGATGGGAAACCAGGACCTCCTGGAAGTCAGGGAGAAAGTGGTCGACCAG
GTCCTCCAGGCTCACCTGGTCCCCGAGGTCAGCCTGGAGTCATGGGCTTCCCTGG
TCCTAAAGGAAATGACGGTGCTCCTGGAAAGAATGGAGAAAGAGGTGGCCCTGGA
GGTCCCGGCCTTCCGGGTCCTCCTGGAAAGAATGGTGAGACAGGACCTCAGGGTC
CCCCAGGACCTACTGGGCCAGGTGGTGACAAAGGAGACACAGGACCCCCTGGTCA
ACAAGGATTACAAGGCTTGCCTGGAACCAGTGGTCCTCCAGGAGAAAATGGAAAA
CCTGGTGAACCCGGCCCAAAAGGTGAAGCTGGTGCACCTGGAATTCCAGGAGGCA
AGGGTGATTCTGGTGCCCCCGGTGAACGTGGACCTCCTGGTGCAGTAGGTCCCTC
AGGACCTAGAGGTGGAGCTGGCCCCCCTGGTCCCGAAGGAGGAAAGGGCCCTGCT
```

Figure 11 A                         1

GGTCCCCCTGGGCCGCCTGGTGCCGCTGGTACACCTGGTCTGCAAGGGATGCCTG
GAGAAAGAGGAGGTTCTGGAGGCCCCGGCCCAAAGGGTGACAAGGGTGACCCTGG
CGGTTCAGGTGCTGATGGTGCTCCAGGAAAAGATGGTCCAAGGGGTCCTACTGGT
CCCATTGGTCCCCCTGGTCCAGCTGGTCAGCCTGGAGATAAGGGTGAAAGTGGTG
CCCCTGGACTTCCTGGTATAGCTGGTCCTCGTGGTGGCCCTGGTGAGAGAGGTGA
ACATGGGCCACCAGGACCTGCCGGCTTCCCTGGTGCTCCTGGCCAGAACGGTGAG
CCTGGTGCCAAAGGAGAAAGAGGCGCTCCTGGTGAGAAAGGTGAAGGAGGACCTC
CTGGGATTGCAGGACAGCCCGGAGGCACTGGGCCTCCTGGTCCCCCTGGTCCCCA
AGGTGTCAAAGGTGAACGTGGCAGTCCTGGTGGTCCTGGTGCTGCTGGGTTCCCC
GGTGGTCGTGGTCTTCCTGGTCCTCCTGGCAGTAACGGTAACCCAGGCCCCCCTG
GCTCCAGTGGTCCTCCAGGCAAAGATGGTCCCCCAGGTCCACCTGGTAGCAGTGG
TGCTCCTGGCAGCCCTGGAGTATCTGGACCGAAAGGTGATGCCGGTCAACCAGGT
GAAAAAGGATCACCTGGCCCCCAGGGCCCTCCGGGAGCTCCAGGCCCAGGTGGAA
TTTCAGGGATTACTGGAGCACGAGGTCTCGCAGGCCCACCAGGCATGCCAGGTGC
TAGGGGAAGCCCTGGCCCACAGGGCGTCAAGGGTGAAAATGGAAAACCAGGACCT
AGTGGTCTCAATGGAGAACGTGGTCCTCCTGGACCCCAGGGTCTTCCTGGTCTGG
CTGGTGCAGCTGGTGAACCTGGACGAGATGGAAACCCTGGATCAGATGGTCTGCC
AGGCCGAGACGGAGCTCCCGGTAGCAAGGGCGATCGTGGTGAAAATGGCTCTCCT
GGTGCCCCTGGTGCTCCTGGTCACCCAGGCCCACCTGGCCCTGTTGGTCCTGCTG
GAAAGAATGGTGACAGAGGAGAAACTGGCCCTGCTGGTCCTGCTGGTGCTCCAGG
TCCTGCTGGTTCAAGAGGTGCTCCTGGTCCCCAAGGCCCACGCGGTGACAAAGGT
GAAACCGGTGAACGTGGTGCTAATGGCATCAAAGGACATCGAGGATTCCCTGGTA
ATCCAGGTGCCCCAGGTTCTCCAGGTCCCGCTGGTCACCAAGGTGCAGTAGGTAG
CCCAGGACCTGCAGGCCCCAGAGGACCTGTTGGACCGAGTGGGCCCCCTGGCAAA
GATGGAGCAAGTGGACACCCTGGTCCCATTGGACCACCAGGGCCTCGAGGTAACA
GAGGTGAAAGAGGATCTGAGGGCTCCCCAGGCCATCCAGGACAACCAGGCCCTCC
TGGACCCCCTGGTGCCCCTGGTCCATGTTGTGGTGGTGGGGCTGCTGCCATCGCT
GGTGTTGGAGGTGAAAAAGCTGGTGGTTTTGCCCCATATTATGGAGATGAACCAA
TGGATTTCAAAATCAACACCGACGAGATTATGACTTCACTTAAATCCGTCAACGG
ACAAATAGAAAGCCTCATTAGTCCCGATGGTTCTCGTAAAAACCCTGCTCGTAAC
TGCAGAGACCTAAAATTCTGCCATCCTGAGCTCAAGAGCGGAGAATATTGGGTTG
ATCCTAACCAAGGCTGCAAAATGGATGCTATTAAAGTATTTTGTAACATGGAAAC
TGGGGAAACATGCATAAGTGCCAGTCCTTCTACTGTTCCACGTAAGAACTGGTGG
ACAGATTCTGGTGCTGAGAAGAAATATGTTTGGTTTGGAGAATCCATGAATGGTG
GTTTTCAGTTTAGCTATGGCAATCCTGAACTTCCTGAAGATGTCCTTGATGTCCA
GTTGGCATTCCTTCGACTTCTCTCTAGCCGAGCTTCCCAGAACATCACATATCAC
TGCAAGAATAGCATTGCGTACATGGAACATGCCAGTGGGAATGTAAAGAAAGCCT
TGAGGCTGATGGGATCAAATGAAGGTGAATTCAAGGCTGAAGGAAATAGCAAATT
CACATACACCGTTCTGGAGGATGGTTGCACTAAACACACTGGGGAATGGGGCAAG
ACAGTCTTCGAATATCGAACACGCAAGGCTGTGAGACTACCTATTGTAGATATTG

Figure 11B

CACCCTATGATATTGGTGGTCCTGATCAAGAATTTGGTGCGGACATTGGCCCTGT
TTGCTTTTTATAAACCAAACCTGAATTC

Figure 11 C

3

```
Met Met Ser Phe Val Gln Lys Gly Thr Trp Leu Leu Phe Ala
Leu Leu His Pro Thr Val Ile Leu Ala Gln Gln Gln Glu Ala
Ile Glu Gly Gly Cys Ser His Leu Gly Gln Ser Tyr Ala Asp
Arg Asp Val Trp Lys Pro Glu Pro Cys Gln Ile Cys Val Cys
Asp Ser Gly Ser Val Leu Cys Asp Asp Ile Ile Cys Asp Asp
Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro Phe Gly Glu
Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr Arg
Pro Pro Asn Gly His Gly Pro Gln Gly Pro Lys Gly Asp Pro
Gly Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Leu
Pro Gly Gln Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly
Ile Cys Glu Ser Cys Pro Thr Gly Gly Gln Asn Tyr Ser Pro
Gln Tyr Glu Ser Tyr Asp Val Lys Ala Gly Val Ala Gly Gly
Gly Ile Gly Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly Pro
Pro Gly Pro Pro Gly Val Ser Gly His Pro Gly Ala Pro Gly
Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala
Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro
Ser Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly
Arg Pro Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Leu Lys
Gly Pro Ala Gly Met Pro Gly Phe Pro Gly Met Lys Gly His
Arg Gly Phe Asp Gly Arg Asn Gly Glu Lys Gly Asp Thr Gly
Ala Pro Gly Leu Lys Gly Glu Asn Gly Leu Pro Gly Glu Asn
Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala Pro Gly Glu
Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly
Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro
Gly Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala
Lys Gly Glu Val Gly Pro Ala Gly Ser Pro Gly Pro Ser Gly
Ser Pro Gly Gln Arg Gly Glu Pro Gly Pro Gln Gly His Ala
Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ser Asn Gly Ser
Pro Gly Gly Lys Gly Glu Met Gly Pro Ala Gly Ile Pro Gly
Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro Gly Pro Pro
Gly Thr Asn Gly Ala Pro Gly Gln Arg Gly Ala Ala Gly Glu
Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly
Glu Arg Gly Glu Ala Gly Ser Pro Gly Ile Pro Gly Pro Lys
Gly Glu Asp Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala
Asn Gly Leu Pro Gly Ala Ala Gly Glu Arg Gly Met Pro Gly
Phe Arg Gly Ala Pro Gly Ala Asn Gly Leu Pro Gly Glu Lys
Gly Pro Ala Gly Glu Arg Gly Gly Pro Gly Pro Ala Gly Pro
Arg Gly Val Ala Gly Glu Pro Gly Arg Asp Gly Val Pro Gly
Gly Pro Gly Leu Arg Gly Met Pro Gly Ser Pro Gly Gly Pro
```

Figure 12 A                                                        1

```
Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu
Ser Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly
Gln Pro Gly Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp
Gly Ala Pro Gly Lys Asn Gly Glu Arg Gly Gly Pro Gly Gly
Pro Gly Leu Pro Gly Pro Pro Gly Lys Asn Gly Glu Thr Gly
Pro Gln Gly Pro Pro Gly Pro Thr Gly Pro Gly Gly Asp Lys
Gly Asp Thr Gly Pro Pro Gly Gln Gln Gly Leu Gln Gly Leu
Pro Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly
Glu Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro
Gly Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro
Pro Gly Ala Val Gly Pro Ser Gly Pro Arg Gly Gly Ala Gly
Pro Pro Gly Pro Glu Gly Gly Lys Gly Pro Ala Gly Pro Pro
Gly Pro Pro Gly Ala Ala Gly Thr Pro Gly Leu Gln Gly Met
Pro Gly Glu Arg Gly Gly Ser Gly Gly Pro Gly Pro Lys Gly
Asp Lys Gly Asp Pro Gly Gly Ser Gly Ala Asp Gly Ala Pro
Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly Pro
Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Ser Gly
Ala Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro
Gly Glu Arg Gly Glu His Gly Pro Pro Gly Pro Ala Gly Phe
Pro Gly Ala Pro Gly Gln Asn Gly Glu Pro Gly Ala Lys Gly
Glu Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro
Gly Ile Ala Gly Gln Pro Gly Gly Thr Gly Pro Pro Gly Pro
Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly Ser Pro Gly
Gly Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly Leu Pro
Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser
Ser Gly Pro Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly
Ser Ser Gly Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys
Gly Asp Ala Gly Gln Pro Gly Glu Lys Gly Ser Pro Gly Pro
Gln Gly Pro Pro Gly Ala Pro Gly Pro Gly Gly Ile Ser Gly
Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
Gly Ala Arg Gly Ser Pro Gly Pro Gln Gly Val Lys Gly Glu
Asn Gly Lys Pro Gly Pro Ser Gly Leu Asn Gly Glu Arg Gly
Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Ala Ala
Gly Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu
Pro Gly Arg Asp Gly Ala Pro Gly Ser Lys Gly Asp Arg Gly
Glu Asn Gly Ser Pro Gly Ala Pro Gly Ala Pro Gly His Pro
Gly Pro Pro Gly Pro Val Gly Pro Ala Gly Lys Asn Gly Asp
Arg Gly Glu Thr Gly Pro Ala Gly Pro Ala Gly Ala Pro Gly
Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg
Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Asn Gly Ile
```

Figure 12 B

2

```
Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly
Ser Pro Gly Pro Ala Gly His Gln Gly Ala Val Gly Ser Pro
Gly Pro Ala Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro
Pro Gly Lys Asp Gly Ala Ser Gly His Pro Gly Pro Ile Gly
Pro Pro Gly Pro Arg Gly Asn Arg Gly Glu Arg Gly Ser Glu
Gly Ser Pro Gly His Pro Gly Gln Pro Gly Pro Pro Gly Pro
Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Gly Ala Ala Ala
Ile Ala Gly Val Gly Gly Glu Lys Ala Gly Gly Phe Ala Pro
Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu
Ser Leu Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg
Asn Cys Arg Asp Leu Lys Phe Cys His Pro Glu Leu Lys Ser
Gly Glu Tyr Trp Val Asp Pro Asn Gln Gly Cys Lys Met Asp
Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly Glu Thr Cys
Ile Ser Ala Ser Pro Ser Thr Val Pro Arg Lys Asn Trp Trp
Thr Asp Ser Gly Ala Glu Lys Lys Tyr Val Trp Phe Gly Glu
Ser Met Asn Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg
Leu Leu Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys
Lys Asn Ser Ile Ala Tyr Met Glu His Ala Ser Gly Asn Val
Lys Lys Ala Leu Arg Leu Met Gly Ser Asn Glu Gly Glu Phe
Lys Ala Glu Gly Asn Ser Lys Phe Thr Tyr Thr Val Leu Glu
Asp Gly Cys Thr Lys His Thr Gly Glu Trp Gly Lys Thr Val
Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro Ile Val
Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
Gly Ala Asp Ile Gly Pro Val Cys Phe Leu
```

Figure 12 C

3

→Section

```
                         (1) 1         10        20        30        43
BOV C1A1 (SW:P02453)     (1) -------------------------------------------
BOV C1A1 (Miller, 1984)  (1) -------------------------------------------
BOV C1A1 (Fibrogen)      (1) MFSFVDLRLLLLLLAATALLTHGQEEGQEEGQEEDIPPVTCVQN
HU C1A1 (GB:COL1A1)      (1) MFSFVDLRLLLLLLAATALLTHGQEEGQVEGQDEDIPPITCVQN
CANIS C1A1 (GB:AF153062) (1) MFSFVDLRLLLLLLAATALLTHGQEEG----QEEDIPPVTCVQN
MUS C1A1 (GB:MMU08020)   (1) MFSFVDLRLLLLLLGATALLTHGQEDIP-------E--VSCIHN
CYNPS C1A1 (GB:AB015438) (1) MFSFVDNRLLVLLAACVLLVRALDQEDIESG---L----CHQE
RANA C1A1 (GB:AB015440)  (1) MFSFVDTRLLLLVIAATILVAKCQGEDDLGYS---G----CVVD
Consensus                (1) MFSFVDLRLLLLLLAATALLTHGQEE      I    VTCVQN
```
————————————————————————————————— Section 2

```
                        (44) 44     50        60        70        86
BOV C1A1 (SW:P02453)     (1) -------------------------------------------
BOV C1A1 (Miller, 1984)  (1) -------------------------------------------
BOV C1A1 (Fibrogen)     (44) GLRYHDRDVWKPVPCQICVCDNGNVLCDDVICDELK-DCPNAK
HU C1A1 (GB:COL1A1)     (44) GLRYHDRDVWKPEPCRICVCDNGKVLCDDVICDETK-NCPGAE
CANIS C1A1 (GB:AF153062)(40) GLRYYDRDVWKPEACRICVCDNGNVLCDDVICDETK-NCPGAQ
MUS C1A1 (GB:MMU08020)  (35) GLRVPNGETWKPEVCLICICHNGTAVCDDVQCNEEL-DCPNPQ
CYNPS C1A1 (GB:AB015438)(37) GTTYSDKDVWKPEPCVICVCDNGNIMCDDVTCGDYPVDCPNAE
RANA C1A1 (GB:AB015440) (37) GRTYNDKDVWKPEACQICVCDEGTILCDEVICEDIG-DCPNPE
Consensus               (44) GLRY DRDVWKPE C ICVCDNG VLCDDVICDE   DCPNA
```
————————————————————————————————— Section 3

```
                        (87) 87          100       110       129
BOV C1A1 (SW:P02453)     (1) -------------------------------------------
BOV C1A1 (Miller, 1984)  (1) -------------------------------------------
BOV C1A1 (Fibrogen)     (86) VPTDECCPVCPEGQESPTDQETTGVEGPKGDTGPRGPRGPAGP
HU C1A1 (GB:COL1A1)     (86) VPEGECCPVCPDGSESPTDQETTGVEGPKGDTGPRGPRGPAGP
CANIS C1A1 (GB:AF153062)(82) VPPGECCPVCPDGEASPTDQETTGVEGPKGDTGPRGPRGPAGP
MUS C1A1 (GB:MMU08020)  (77) RREGGCCAFCPEEYVS-PNSEDVGVEGPKGGPGPQGPRGPVGP
CYNPS C1A1 (GB:AB015438)(80) IPFGECCPVCPDGDGT-SYSEQTGVEGPKGEVGPKGDRGLPGP
RANA C1A1 (GB:AB015440) (79) IPMGECCPVCGEGQ----YQTGSVVEGPKGETGPRGERGPPGA
Consensus               (87) VP GECCPVCPDG  S T QE TGVEGPKGDTGPRGPRGP GP
```
————————————————————————————————— Section 4

```
                       (130) 130       140       150       160       172
BOV C1A1 (SW:P02453)     (1) -------------------------------------QLSYGYDEKS
BOV C1A1 (Miller, 1984)  (1) ---------------------------------------------
BOV C1A1 (Fibrogen)    (129) PGRDGIPGQPGLPGPPGPPGPPGPPGLGGNFAPQLSYGYDEKS
HU C1A1 (GB:COL1A1)    (129) PGRDGIPGQPGLPGPPGPPGPPGPPGLGGNFAPQLSYGYDEKS
CANIS C1A1 (GB:AF153062)(125) PGRDGIPGQPGLPGPPGPPGPPGPPGLGGNFAPQMSYGYDEKS
MUS C1A1 (GB:MMU08020) (119) PGRDGIPGQPGLPGPPGPPGPPGPPGLGGNFASQMSYGYDEKS
CYNPS C1A1 (GB:AB015438)(122) PGRDGN---PGLPGPPGPPGPPG---LGGNFAPQMSYGYDEKS
RANA C1A1 (GB:AB015440)(118) PGRDGIPGQPGIPGPPGPPGPAG---LGGNFAPQMSYGYDEKS
Consensus              (130) PGRDGIPGQPGLPGPPGPPGPPGPPGLGGNFAPQMSYGYDEKS
```

FIGURE 13A

Section 5

|  | (173) | 173 · | 180 | 190 | 200 | 215 |

BOV C1A1 (SW:P02453)  (11) TG-ISVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS
BOV C1A1 (Miller, 1984)  (1) -------GPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS
BOV C1A1 (Fibrogen) (172) TG-ISVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS
HU C1A1 (GB:COL1A1) (172) TGGISVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS
CANIS C1A1 (GB:AF153062) (168) TGGISVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS
MUS C1A1 (GB:MMU08020) (162) AG-VSVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGGS
CYNPS C1A1 (GB:AB015438) (159) AG-ISVPGPMGPMGPRGPPGPSGSPGPQGFQGPSGEPGEPGAA
RANA C1A1 (GB:AB015440) (158) AG-ISMPGPMGPMGPRGPPGPSGSPGPQGFQGPPGEPGEPGAA
Consensus (173) TG ISVPGPMGPSGPRGLPGPPGAPGPQGFQGPPGEPGEPGAS

Section 6

|  | (216) | 216 | 230 | 240 | 258 |

BOV C1A1 (SW:P02453) (53) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
BOV C1A1 (Miller, 1984) (37) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
BOV C1A1 (Fibrogen) (214) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
HU C1A1 (GB:COL1A1) (215) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
CANIS C1A1 (GB:AF153062) (211) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
MUS C1A1 (GB:MMU08020) (204) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG
CYNPS C1A1 (GB:AB015438) (201) GALGPRGLPGPPGKNGDDGESGKPGRPGERGPSGPQGARGLPG
RANA C1A1 (GB:AB015440) (200) GAMGPRGPPGPPGKNGEDGEAGKPGRPGERGPPGPQGARGLPG
Consensus (216) GPMGPRGPPGPPGKNGDDGEAGKPGRPGERGPPGPQGARGLPG

Section 7

|  | (259) | 259 | 270 | 280 | 290 | 301 |

BOV C1A1 (SW:P02453) (96) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
BOV C1A1 (Miller, 1984) (80) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
BOV C1A1 (Fibrogen) (257) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
HU C1A1 (GB:COL1A1) (258) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
CANIS C1A1 (GB:AF153062) (254) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
MUS C1A1 (GB:MMU08020) (247) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ
CYNPS C1A1 (GB:AB015438) (244) TAGLPGMKGHRGFNGLDGAKGDNGPAGPKGEPGNPGENGAPGQ
RANA C1A1 (GB:AB015440) (243) TAGLPGMKGHRGFNGLDGAKGDTGPAGPKGEPGNPGENGAPGQ
Consensus (259) TAGLPGMKGHRGFSGLDGAKGDAGPAGPKGEPGSPGENGAPGQ

Section 8

|  | (302) | 302 | 310 | 320 | 330 | 344 |

BOV C1A1 (SW:P02453) (139) MGPRGLPG-----------------------------------
BOV C1A1 (Miller, 1984) (123) MGPRGLPGERGRPGAPGPAGARGNDGATGAAGPPGPTGPAGPP
BOV C1A1 (Fibrogen) (300) MGPRGLPGERGRPGAPGPAGARGNDGATGAAGPPGPTGPAGPP
HU C1A1 (GB:COL1A1) (301) MGPRGLPGERGRPGAPGPAGARGNDGATGAAGPPGPTGPAGPP
CANIS C1A1 (GB:AF153062) (297) MGPRGLPGERGRPGAPGPAGARGNDGATGAAGPPGPTGPAGPP
MUS C1A1 (GB:MMU08020) (290) MGPRGLPGERGRPGPPGTAGARGNDGAVGAAGPPGPTGPTGPP
CYNPS C1A1 (GB:AB015438) (287) AGPRGLPGERGRPGAPGPAGARGNDGSPGAAGPPGPTGPTGPP
RANA C1A1 (GB:AB015440) (286) VGPRGLPGERGRPGPSGPAGARGNDGTPGAAGPPGPTGPTGPP
Consensus (302) MGPRGLPGERGRPGAPGPAGARGNDGATGAAGPPGPTGPAGPP

*FIGURE 13B*

Section 9

```
                        (345) 345      350         360          370            387
BOV C1A1 (SW:P02453)    (147) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984) (166) GFPGAVGAKGEGGPQGPRGSEGPQGVRGEPGPPGPAGAAGPAG
BOV C1A1 (Fibrogen)     (343) GFPGAVGAKGEGGPQGPRGSEGPQGVRGEPGPPGPAGAAGPAG
HU C1A1 (GB:COL1A1)     (344) GFPGAVGAKGEAGPQGPRGSEGPQGVRGEPGPPGPAGAAGPAG
CANIS C1A1 (GB:AF153062)(340) GFPGAVGAKGEAGPQGRRGSEGPQGVRGEPGPPGPAGAAGPAG
MUS C1A1 (GB:MMU08020)  (333) GFPGAVGAKGEAGPQGRRGSEGPQGVRGEPGPPGPAGAAGPAG
CYNPS C1A1 (GB:AB015438)(330) GFPGAVGAKGDAGPQGRRGSEGPQGARGEPGAPGPAGAAGPSG
RANA C1A1 (GB:AB015440) (329) GFPGSVGPKGDAGPQGSRGPDGPQGARGEPGAPGQAGPAGSAG
Consensus               (345) GFPGAVGAKGEAGPQGARGSEGPQGVRGEPGPPGPAGAAGPAG
```

Section 10

```
                        (388) 388        400        410          420          430
BOV C1A1 (SW:P02453)    (147) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984) (209) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPSGPPGP
BOV C1A1 (Fibrogen)     (386) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPSGPPGP
HU C1A1 (GB:COL1A1)     (387) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPGGPPGP
CANIS C1A1 (GB:AF153062)(383) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPSGPPGP
MUS C1A1 (GB:MMU08020)  (376) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPSGPPGP
CYNPS C1A1 (GB:AB015438)(373) NPGTDGQPGBKGATGBPGIAGAPGFPGARGAPGPQGPBGAPGP
RANA C1A1 (GB:AB015440) (372) NPGTDGQPGAKGATGAPGIAGAPGFPGARGAPGPQGPGGSPGP
Consensus               (388) NPGADGQPGAKGANGAPGIAGAPGFPGARGPSGPQGPSGPPGP
```

Section 11 .

```
                        (431) 431        440         450          460          473
BOV C1A1 (SW:P02453)    (147) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984) (252) KGNSGEPGAPGSKGDTGAKGEPGPTGIQGPPGPAGEEGKRGAR
BOV C1A1 (Fibrogen)     (429) KGNSGEPGAPGSKGDTGAKGEPGPTGIQGPPGPAGEEGKRGAR
HU C1A1 (GB:COL1A1)     (430) KGNSGEPGAPGSKGDTGAKGEPGPVGIQGPPGPAGEEGKRGAR
CANIS C1A1 (GB:AF153062)(426) KGNSGEPGAPGNKGDTGAKGEPGPTGIQGPPGPAGEEGKRGAR
MUS C1A1 (GB:MMU08020)  (419) KGNSGEPGAPGNKGDTGAKGEPGATGVQGPPGPAGEEGKRGAR
CYNPS C1A1 (GB:AB015438)(416) KGNNGEPGAQGNKGBPGAKGEPGPAGVQGPPGPSGEEGKRGSR
RANA C1A1 (GB:AB015440) (415) KGNNGEPGAQGNKGBPGAKGBSGPAGSQGPPGPPGEEGKRGSR
Consensus               (431) KGNSGEPGAPGNKGDTGAKGBPGPTGIQGPPGPAGEEGKRGAR
```

Section 12

```
                        (474) 474      480          490          500          516
BOV C1A1 (SW:P02453)    (147) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984) (295) GEPGPAGLPGPPGERGGPGSRGFPGADGVAGPKGPAGERGAPG
BOV C1A1 (Fibrogen)     (472) GEPGPAGLPGPPGERGGPGSRGFPGADGVAGPKGPAGERGAPG
HU C1A1 (GB:COL1A1)     (473) GEPGPTGLPGPPGERGGPGSRGFPGADGVAGPKGPAGERGAPG
CANIS C1A1 (GB:AF153062)(469) GEPGPTGLPGPPGERGGPGSRGFPGADGVAGPKGPAGERGAPG
MUS C1A1 (GB:MMU08020)  (462) GEPGPSGLPGPPGERGGPGSRGFPGADGVAGPKGPSGERGAPG
CYNPS C1A1 (GB:AB015438)(459) GEPGPAGPPGPAGERGGPGSRGFPGSDGASGPKGAPGERGSVG
RANA C1A1 (GB:AB015440) (458) GEPGPSGPPGPAGERGAPGSRGFPGADGADGPKGPPGERGPVG
Consensus               (474) GEPGPAGLPGPPGERGGPGSRGFPGADGVAGPKGPAGERGAPG
```

FIGURE 13C

43/49

Section 13

```
                          (517) 517              530           540                    559
          BOV C1A1 (SW:P02453) (147) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
        BOV C1A1 (Miller, 1984) (338) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
          BOV C1A1 (Fibrogen) (515) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
         HU C1A1 (GB:COL1A1) (516) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
      CANIS C1A1 (GB:AF153062) (512) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
       MUS C1A1 (GB:MMU08020) (505) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
      CYNPS C1A1 (GB:AB015438) (502) PAGPKGSTGESGRPGEPGLPGAKGLTGSPGSPGPDGKTGPAGA
       RANA C1A1 (GB:AB015440) (501) SAGPKGSPGESGRPGEPGLPGAKGLTGSPGSPGPDGKTGPAGA
                   Consensus (517) PAGPKGSPGEAGRPGEAGLPGAKGLTGSPGSPGPDGKTGPPGP
```

Section 14

```
                          (560) 560         570         580         590         602
          BOV C1A1 (SW:P02453) (147) - - - - - - - - - - - - - - - - - - - - FPGPKGAAGEPGKAGERGVP
        BOV C1A1 (Miller, 1984) (381) AGQNGRPGPAGPPGARGQAGVMGFPGPKGAAGEPGKAGERGVP
          BOV C1A1 (Fibrogen) (558) AGQDGRPGPPGPPGARGQAGVMGFPGPKGAAGEPGKAGERGVP
         HU C1A1 (GB:COL1A1) (559) AGQDGRPGPPGPPGARGQAGVMGFPGPKGAAGEPGKAGERGVP
      CANIS C1A1 (GB:AF153062) (555) AGQDGRPGPPGPPGARGQAGVMGFPGPKGAAGEPGKAGERGVP
       MUS C1A1 (GB:MMU08020) (548) AGQDGRPGPAGPPGARGQAGVMGFPGPKGTAGEPGKAGERGLP
      CYNPS C1A1 (GB:AB015438) (545) AGQDGHPGPPGPSGARGQSGVMGFPGPKGAAGEPGKSGERGVA
       RANA C1A1 (GB:AB015440) (544) PGQDGRPGPPGPPGARGQSGVMGFPGPKGAAGEPGKPGERGVA
                   Consensus (560) AGQDGRPGPPGPPGARGQAGVMGFPGPKGAAGEPGKAGERGVP
```

Section 15

```
                          (603) 603      610         620          630         645
          BOV C1A1 (SW:P02453) (167) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
        BOV C1A1 (Miller, 1984) (424) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
          BOV C1A1 (Fibrogen) (601) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
         HU C1A1 (GB:COL1A1) (602) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
      CANIS C1A1 (GB:AF153062) (598) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
       MUS C1A1 (GB:MMU08020) (591) GPPGAVGPAGKDGEAGAQGAPGPAGPAGERGEQGPAGSPGFQG
      CYNPS C1A1 (GB:AB015438) (588) GPPGATGAPGKDGEAGAQGPPGPSGPSGERGEQGPAGSPGFQG
       RANA C1A1 (GB:AB015440) (587) GPPGAVGAPGKDGEAGAQGPPGPAGPAGERGEQGPAGPPGFQG
                   Consensus (603) GPPGAVGPAGKDGEAGAQGPPGPAGPAGERGEQGPAGSPGFQG
```

Section 16

```
                          (646) 646          660         670          688
          BOV C1A1 (SW:P02453) (210) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
        BOV C1A1 (Miller, 1984) (467) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
          BOV C1A1 (Fibrogen) (644) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
         HU C1A1 (GB:COL1A1) (645) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
      CANIS C1A1 (GB:AF153062) (641) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
       MUS C1A1 (GB:MMU08020) (634) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
      CYNPS C1A1 (GB:AB015438) (631) LPGSPGPAGEAGKPGEQGAPGDAGGPGPSGPRGERGFPGERGG
       RANA C1A1 (GB:AB015440) (630) LPGSPGAPGESGKPGEQGAPGDVGPSGPAGSRGERGFPGERGA
                   Consensus (646) LPGPAGPPGEAGKPGEQGVPGDLGAPGPSGARGERGFPGERGV
```

FIGURE 13D

```
                                                                          Section 17
                          (689) 689         700        710        720        731
BOV C1A1 (SW:P02453)      (253) EGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
BOV C1A1 (Miller, 1984)   (510) EGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
BOV C1A1 (Fibrogen)       (687) QGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
HU C1A1 (GB:COL1A1)       (688) QGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
CANIS C1A1 (GB:AF153062)  (684) QGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
MUS C1A1 (GB:MMU08020)    (677) QGPPGPAGPRGNNGAPGNDGAKGDTGAPGAPGSQGAPGLQGMP
CYNPS C1A1 (GB:AB015438)  (674) QGPAGAQGPRGSPGSPGNDGAKGEAGAAGAPGGRGPPGLQGMP
RANA C1A1 (GB:AB015440)   (673) IGPPGPQGPRGANGAPGNDGAKGEAGAPGAPGGQGPSGLQGMP
Consensus                 (689) QGPPGPAGPRGANGAPGNDGAKGDAGAPGAPGSQGAPGLQGMP
                                                                          Section 18

                          (732) 732        740        750        760        774
BOV C1A1 (SW:P02453)      (296) GERGAAGLPGPKGDRGDAGPKGADGAPGKDGVRGLTGPIGPPG
BOV C1A1 (Miller, 1984)   (553) GERGAAGLPGPKGDRGDAGPKGADGAPGKDGVRGLTGPIGPPG
BOV C1A1 (Fibrogen)       (730) GERGAAGLPGPKGDRGDAGPKGADGAPGKDGVRGLTGPIGPPG
HU C1A1 (GB:COL1A1)       (731) GERGAAGLPGPKGDRGDAGPKGADGSPGKDGVRGLTGPIGPPG
CANIS C1A1 (GB:AF153062)  (727) GERGAAGLPGPKGDRGDAGPKGADGSPGKDGVRGLTGPIGPPG
MUS C1A1 (GB:MMU08020)    (720) GERGAAGLPGPKGDRGDAGPKGADGSPGKDGARGLTGPIGPPG
CYNPS C1A1 (GB:AB015438)  (717) GERGSAGMPGAKGDRGDAGTKGADGAPGKDGARGLTGPIGPPG
RANA C1A1 (GB:AB015440)   (716) GERGAGGLPGAKGDRGDQGPKGADGAPGKDGVRGLTGPIGPPG
Consensus                 (732) GERGAAGLPGPKGDRGDAGPKGADGAPGKDGVRGLTGPIGPPG
                                                                          Section 19

                          (775) 775    780        790        800        817
BOV C1A1 (SW:P02453)      (339) PAGAPGDKGEAGPSG---PAGTRGAPGDRGEPGPPGPAGFAGP
BOV C1A1 (Miller, 1984)   (596) PAGAPGDKGEAGPSGPAGPTGARGAPGDRGEPGPPGPAGFAGP
BOV C1A1 (Fibrogen)       (773) PAGAPGDKGEAGPSGPAGPTGARGAPGDRGEPGPPGPAGFAGP
HU C1A1 (GB:COL1A1)       (774) PAGAPGDKGESGPSGPAGPTGARGAPGDRGEPGPPGPAGFAGP
CANIS C1A1 (GB:AF153062)  (770) PAGAPGDKGEAGPSGPAGPTGARGAPGDRGEPGPPGPAGFAGP
MUS C1A1 (GB:MMU08020)    (763) PAGAPGDKGEAGPSGPPGPTGARGAPGDRGEAGPPGPAGFAGP
CYNPS C1A1 (GB:AB015438)  (760) PSGAPGDKGEGGPSGPAGPTGARGSPGERGEPGAPGPAGICGP
RANA C1A1 (GB:AB015440)   (759) PGGAPGDKGEAGPAGPAGPTGSRGAPGERGEPGPSGPAGFAGP
Consensus                 (775) PAGAPGDKGEAGPSGPAGPTGARGAPGDRGEPGPPGPAGFAGP
                                                                          Section 20

                          (818) 818         830        840        850        860
BOV C1A1 (SW:P02453)      (379) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPAGPPGPIGNVGAP
BOV C1A1 (Miller, 1984)   (639) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPAGPPGPIGNVGAP
BOV C1A1 (Fibrogen)       (816) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPAGPPGPIGNVGAP
HU C1A1 (GB:COL1A1)       (817) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPAGPPGPIGNVGAP
CANIS C1A1 (GB:AF153062)  (813) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPTGPPGPIGNVGAP
MUS C1A1 (GB:MMU08020)    (806) PGADGQPGAKGEPGDTGVKGDAGPPGPAGPAGPPGPIGNVGAP
CYNPS C1A1 (GB:AB015438)  (803) PGADGQPGAKGESGDAGPKGDAGAPGPAGPTGAPGPAGNVGAP
RANA C1A1 (GB:AB015440)   (802) PGADGQPGAKGEQGDAGPKGDAGPPGAAGPTGAPGPAGAVGAT
Consensus                 (818) PGADGQPGAKGEPGDAGAKGDAGPPGPAGPAGPPGPIGNVGAP
```

Figure 13E

```
                                                                        Section 21
              (861) 861        870         880         890          903
 BOV C1A1 (SW:P02453) (422) GPKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
 BOV C1A1 (Miller, 1984) (682) GPKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
 BOV C1A1 (Fibrogen) (859) GPKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
 HU C1A1 (GB:COL1A1) (860) GAKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
 CANIS C1A1 (GB:AF153062) (856) GPKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
 MUS C1A1 (GB:MMU08020) (849) GPKGPRGAAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPVG
 CYNPS C1A1 (GB:AB015438) (846) GPKGTRGAAGPPGATGFPGAAGRLGPPGPSGNAGPPGPPGPGG
 RANA C1A1 (GB:AB015440) (845) GPKGARGPAGPPGSTGFPGAAGRVGPPGPSGNAGPPGPSGPAG
 Consensus (861) GPKGARGSAGPPGATGFPGAAGRVGPPGPSGNAGPPGPPGPAG
                                                                        Section 22
              (904) 904     910         920         930          946
 BOV C1A1 (SW:P02453) (465) KEGSKGPRGETGPAGRPGEVGPPGPPGPAGEKGAPGADGPAGA
 BOV C1A1 (Miller, 1984) (725) KEGSKGPRGETGPAGRPGEVGPPGPPGPAGEKGAPGADGPAGA
 BOV C1A1 (Fibrogen) (902) KEGSKGPRGETGPAGRPGEVGPPGPPGPAGEKGAPGADGPAGA
 HU C1A1 (GB:COL1A1) (903) KEGGKGPRGETGPAGRPGEVGPPGPPGPAGEKGSPGADGPAGA
 CANIS C1A1 (GB:AF153062) (899) KEGGKGARGETGPAGRPGEVGPPGPPGPAGEKGSPGADGPAGA
 MUS C1A1 (GB:MMU08020) (892) KEGGKGPRGETGPAGRPGEVGPPGPPGPAGEKGSPGADGPAGS
 CYNPS C1A1 (GB:AB015438) (889) KEGAKGSRGETGPAGRSGEPGPAGPPGPSGEKGSPGSDGPAGA
 RANA C1A1 (GB:AB015440) (888) KEGQKGPRGETGPAGRPGEPGAAGPPGPSGEKGSPGSDGPAGA
 Consensus (904) KEGSKGPRGETGPAGRPGEVGPPGPPGPAGEKGSPGADGPAGA
                                                                        Section 23
              (947) 947       960         970          989
 BOV C1A1 (SW:P02453) (508) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 BOV C1A1 (Miller, 1984) (768) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 BOV C1A1 (Fibrogen) (945) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 HU C1A1 (GB:COL1A1) (946) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 CANIS C1A1 (GB:AF153062) (942) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 MUS C1A1 (GB:MMU08020) (935) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
 CYNPS C1A1 (GB:AB015438) (932) PGIPGPQGIAGQRGVVGLPGQRGERGFSGLPGPAGEPGKQGPS
 RANA C1A1 (GB:AB015440) (931) PGIPGPQGIAGTRGTVGLPGQRGERGFPGLPGPTGEPGKQGSS
 Consensus (947) PGTPGPQGIAGQRGVVGLPGQRGERGFPGLPGPSGEPGKQGPS
                                                                        Section 24
              (990) 990       1000        1010        1020         1032
 BOV C1A1 (SW:P02453) (551) GASGERGPPGPMGPPGLAGPPGESGREGAPGAEGSPGRDGSPG
 BOV C1A1 (Miller, 1984) (811) GASGERGPPGPMGPPGLAGPPGESGREGAPGAEGSPGRDGSPG
 BOV C1A1 (Fibrogen) (988) GASGERGPPGPMGPPGLAGPPGESGREGAPGAEGSPGRDGSPG
 HU C1A1 (GB:COL1A1) (989) GASGERGPPGPMGPPGLAGPPGESGREGAPAAEGSPGRDGSPG
 CANIS C1A1 (GB:AF153062) (985) GTSGERGPPGPMGPPGLAGPPGESGREGSPGAEGSPGRDGSPG
 MUS C1A1 (GB:MMU08020) (978) GSSGERGPPGPMGPPGLAGPPGESGREGSPGAEGSPGRDGAPG
 CYNPS C1A1 (GB:AB015438) (975) GPNGERGPPGPSGPPGLGGPPGEPGREGSPGSEGAPGRDGSPG
 RANA C1A1 (GB:AB015440) (974) GPSGERGPPGPSGPPGLAGPPGEPGREGSPGSEGSPGRDGSAG
 Consensus (990) GASGERGPPGPMGPPGLAGPPGESGREGAPGAEGSPGRDGSPG
```

FIGURE 13F

Section 25

```
                        (1033) 1033      1040        1050        1060              1075
        BOV C1A1 (SW:P02453) (594) AKGDRGETGPAGAPGPPGAPGAPGPVGPAGKSGDRGETGPAGP
        BOV C1A1 (Miller, 1984) (854) AKGDRGETGPAGPPGAPGAPGAPGPVGPAGKSGDRGETGPAGP
        BOV C1A1 (Fibrogen)(1031) AKGDRGETGPAGPPGAPGAPGAPGPVGPAGKSGDRGETGPAGP
         HU C1A1 (GB:COL1A1)(1032) AKGDRGETGPAGPPGAPGAPGAPGPVGPAGKNGDRGETGPAGP
      CANIS C1A1 (GB:AF153062)(1028) PKGDRGETGPAGPPGAPGAPGAPGPVGPAGKNGDRGETGPAGP
       MUS C1A1 (GB:MMU08020)(1021) AKGDRGETGPAGPPGAPGAPGAPGPVGPAGKNGDRGETGPAGP
     CYNPS C1A1 (GB:AB015438)(1018) PKGDRGENGPSGPPGAPGAPGAPGPAGPAGKNGDRGETGPAGP
      RANA C1A1 (GB:AB015440)(1017) PKGDRGESGPAGPPGAPGAPGAPGPAGPAGKNGDRGETGPAGP
                   Consensus(1033) AKGDRGETGPAGPPGAPGAPGAPGPVGPAGKSGDRGETGPAGP
```

Section 26

```
                        (1076) 1076          1090        1100              1118
        BOV C1A1 (SW:P02453) (637) IGPVGPAGARGPAGPQGPRGBKGZTGZZGBRGIKGHRGFSGLQ
        BOV C1A1 (Miller, 1984) (897) IGPVGPAGARGPAGPQGPRGDKGETGEEGDRGIKGHRGFSGLQ
        BOV C1A1 (Fibrogen)(1074) AGPIGPVGARGPAGPQGPRGDKGETGEQGDRGIKGHRGFSGLQ
         HU C1A1 (GB:COL1A1)(1075) AGPVGPVGARGPAGPQGPRGDKGETGEQGDRGIKGHRGFSGLQ
      CANIS C1A1 (GB:AF153062)(1071) AGPIGPVGARGPAGPQGPRGDKGETGEQGDRGIKGHRGFSGLQ
       MUS C1A1 (GB:MMU08020)(1064) AGPIGPAGARGPAGPQGPRGDKGETGEQGDRGIKGHRGFSGLQ
     CYNPS C1A1 (GB:AB015438)(1061) AGPAGPSGVRGAPGPAGARGDKGEAGEQGERGMKGHRGFNGMQ
      RANA C1A1 (GB:AB015440)(1060) AGPAGPAGARGPSGPAGARGDKGEAGEQGERGMKGHRGFNDLP
                   Consensus(1076) AGPIGPAGARGPAGPQGPRGDKGETGEQGDRGIKGHRGFSGLQ
```

Section 27

```
                        (1119) 1119          1130        1140        1150          1161
        BOV C1A1 (SW:P02453) (680) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGSPGKDGLNGLPG
        BOV C1A1 (Miller, 1984) (940) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGSPGKDGLNGLPG
        BOV C1A1 (Fibrogen)(1117) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGAPGKDGLNGLPG
         HU C1A1 (GB:COL1A1)(1118) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGSPGKDGLNGLPG
      CANIS C1A1 (GB:AF153062)(1114) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGSPGKDGLNGLPG
       MUS C1A1 (GB:MMU08020)(1107) GPPGSPGSPGEQGPSGASGPAGPRGPPGSSGSTGKDGVNGLPG
     CYNPS C1A1 (GB:AB015438)(1104) GPPGPPGSSGEQGAPGPSGPAGPRGPPGSSGSPGKDGSNGLPG
      RANA C1A1 (GB:AB015440)(1103) GPPGAPGHAGEQGPSGASGPAGPRGPPGSSAGSPGKDGLNGLPG
                   Consensus(1119) GPPGPPGSPGEQGPSGASGPAGPRGPPGSAGSPGKDGLNGLPG
```

Section 28

```
                        (1162) 1162        1170        1180        1190          1204
        BOV C1A1 (SW:P02453) (723) PIGPPGPRGRTGDAGPAGPPGPPGPPGPPGPPSGGYDLSFLPQ
        BOV C1A1 (Miller, 1984) (983) PIGPPGPRGRTGDAGPAGPPGPPGPPGPPGPP----------
        BOV C1A1 (Fibrogen)(1160) PIGPPGPRGRTGDAGPAGPPGPPGPPGPPGPPSGGYDLSFLPQ
         HU C1A1 (GB:COL1A1)(1161) PIGPPGPRGRTGDAGPVGPPGPPGPPGPPGPPSAGFDFSFLPQ
      CANIS C1A1 (GB:AF153062)(1157) PIGPPGPRGRTGDAGPVGPPGPPGPPGPPGPPSGGYDFSFLPQ
       MUS C1A1 (GB:MMU08020)(1150) PIGPPGPRGRTGDSGPAGPPGPPGPPGPPGPPSGGYDFSFMPQ
     CYNPS C1A1 (GB:AB015438)(1147) PIGPPGPRGRNGDVGPAGPPGPPGPPGPPGPPSGGFDFSFMPQ
      RANA C1A1 (GB:AB015440)(1146) PIGPPGPRGRTGDVGPAGPPGPAGPPGPPGPPGGGFDFSFMPQ
                   Consensus(1162) PIGPPGPRGRTGDAGPAGPPGPPGPPGPPGPPSGGFDFSFLPQ
```

Figure 13q

Section 29

```
                        (1205) 1205    1210         1220         1230            1247
BOV C1A1 (SW:P02453)    (766) PPQQZKAHDGGRYY- - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Fibrogen)    (1203) PPQE-KAHDGGRYYRADDANVVRDRDLEVDTTLKSLSQQIENI
HU C1A1 (GB:COL1A1)    (1204) PPQE-KAHDGGRYYRADDANVVRDRDLEVDTTLKSLSQQIENI
CANIS C1A1 (GB:AF153062)(1200) PPQE-KAHDGGRYYRADDANVVRDRDLEVDTTLKSLSQQIENI
MUS C1A1 (GB:MMU08020) (1193) PPQE-KSQDGDRYYRADDANVVRDRDLAVDATLKSLSQQIENI
CYNPS C1A1 (GB:AB015438)(1190) PPEP-KSHGDGRYFRADDANVVRDRDLEVDTTLKSLSAQIENI
RANA C1A1 (GB:AB015440)(1189) PPQE-K- - - -SHHYRADDANAMRDRDMEVDTTLKSLSKQIENI
Consensus              (1205) PPQE  KAHDGGRYYRADDANVVRDRDLEVDTTLKSLSQQIENI
```

Section 30

```
                        (1248) 1248         1260         1270         1280         1290
BOV C1A1 (SW:P02453)    (780) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Fibrogen)    (1245) RSPEGSRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCNLDAIK
HU C1A1 (GB:COL1A1)    (1246) RSPEGSRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCNLDAIK
CANIS C1A1 (GB:AF153062)(1242) RSPEGSRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCNLDAIK
MUS C1A1 (GB:MMU08020) (1235) RSPEGSRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCNLDAIK
CYNPS C1A1 (GB:AB015438)(1232) RSPEGTRKNPARTCRDLKMCHSDWKSGDYWIDPNQGCNLDAIK
RANA C1A1 (GB:AB015440)(1227) RSPEGTRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCTLDAIK
Consensus              (1248) RSPEGSRKNPARTCRDLKMCHSDWKSGEYWIDPNQGCNLDAIK
```

Section 31

```
                        (1291) 1291      1300         1310         1320            1333
BOV C1A1 (SW:P02453)    (780) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Fibrogen)    (1288) VFCNMETGETCVYPTQPSVAQKNWYISKNPKEKRHVWYGESMT
HU C1A1 (GB:COL1A1)    (1289) VFCNMETGETCVYPTQPSVAQKNWYISKNPKDKRHVWFGESMT
CANIS C1A1 (GB:AF153062)(1285) VFCNMETGETCVYPTQPQVAQKNWYISKNPKEKRHVWYGESMT
MUS C1A1 (GB:MMU08020) (1278) VYCNMETGQTCVFPTQPSVPQKNWYISPNPKEKKHVWFGESMT
CYNPS C1A1 (GB:AB015438)(1275) VHCNMETGETCVYPSQASISQKNWYTSKNPREKKHVWFGETMS
RANA C1A1 (GB:AB015440)(1270) VFCNMETGETCVYPTQSTIDQKNWYISNNPREKKHVWFGETMS
Consensus              (1291) VFCNMETGETCVYPTQPSVAQKNWYISKNPKEKKHVWFGESMT
```

Section 32

```
                        (1334) 1334      1340         1350         1360            1376
BOV C1A1 (SW:P02453)    (780) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Fibrogen)    (1331) GGFQFEYGGQGSDPADVAIQLTFLRLMSTEASQNITYHCKNSV
HU C1A1 (GB:COL1A1)    (1332) DGFQFEYGGQGSDPADVAIQLTFLRLMSTEASQNITYHCKNSV
CANIS C1A1 (GB:AF153062)(1328) DGFQFEYGGQGSDPADVAIQLTFLRLMSTEASQNITYHCKNSV
MUS C1A1 (GB:MMU08020) (1321) DGFPFEYGSEGSDPTDVAIQLTFLRLMSTEASQNITYHCKNSV
CYNPS C1A1 (GB:AB015438)(1318) DGFQFEYGGEGSDPADVNIQLTFLRLMATEASQNITYHCKNSV
RANA C1A1 (GB:AB015440)(1313) DGFQFDYGSEGSDPADVNIQLTFLRLMATEASQNITYHCKNSV
Consensus              (1334) DGFQFEYGG  GSDPADVAIQLTFLRLMSTEASQNITYHCKNSV
```

*Figure* 13H

```
                    (1377) 1377            1390         1400                    1419
BOV C1A1 (SW:P02453)  (780) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
   BOV C1A1 (Fibrogen)(1374) AYMDQQTGNLKKALLLQGSNEIEIRAEGNSRFTYSVTYDGCTS
    HU C1A1 (GB:COL1A1)(1375) AYMDQQTGNLKKALLLKGSNEIEIRAEGNSRFTYSVTVDGCTS
  CANIS C1A1 (GB:AF153062)(1371) AYMDQQTGNLKKALLLQGSNEIELRGEGNSRFTYSRVVDGCTS
   MUS C1A1 (GB:MMU08020)(1364) AYMDQQTGNLKKAVLLQGSNEIEIRAEGNSRFTYGVTEDGCTQ
  CYNPS C1A1 (GB:AB015438)(1361) AYMDQETGNLKKAVLLQGSNEIEIRAEGNSRFTYSVIEDGCTQ
   RANA C1A1 (GB:AB015440)(1356) AYMDQETGNLKKALLLQGSNEIEIRAEGNSRFTYSVT DGCTS
               Consensus(1377) AYMDQQTGNLKKALLLQGSNEIEIRAEGNSRFTYSVT DGCTS
```

```
                    (1420) 1420          1430        1440         1450          1462
BOV C1A1 (SW:P02453)  (780) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
   BOV C1A1 (Fibrogen)(1417) HTGAWGKTVIEYKTTKTSRLPIIDVAPLDVGAPDQEFGFDVGP
    HU C1A1 (GB:COL1A1)(1418) HTGAWGKTVIEYKTTKSSRLPIIDVAPLDVGAPDQEFGMDIGP
  CANIS C1A1 (GB:AF153062)(1414) HTGAWGKTVIEYKTTKTSRLPIIDVAPLDIGAPDQEFGLDIGP
   MUS C1A1 (GB:MMU08020)(1407) HTGTWGKTVIEYKTTKTSRLPIIDIAPMDVGTPDQEFGIDIGP
  CYNPS C1A1 (GB:AB015438)(1404) HTGEWGKTVIEYKTTPKTSRLPITDVAPMDIGAPDQEFGVEIGP
   RANA C1A1 (GB:AB015440)(1399) HTGQWGKTVIEYKTPKTSRLPITDVAPMDIGAPDQEFGIDIGP
               Consensus(1420) HTG WGKTVIEYKTTKTSRLPIIDVAPLDVGAPDQEFGIDIGP
```

```
                    (1463) 1461467
BOV C1A1 (SW:P02453)  (780) - - - - -
BOV C1A1 (Miller, 1984)(1015) - - - - -
   BOV C1A1 (Fibrogen)(1460) ACFL-
    HU C1A1 (GB:COL1A1)(1461) VCFL-
  CANIS C1A1 (GB:AF153062)(1457) VCFLY
   MUS C1A1 (GB:MMU08020)(1450) ACFV-
  CYNPS C1A1 (GB:AB015438)(1447) VCFL-
   RANA C1A1 (GB:AB015440)(1442) VCFVY
               Consensus(1463) VCFL
```

FIGURE BJ

SEQUENCE LISTING

<110> FIBROGEN, INC.

<120> ANIMAL COLLAGENS AND GELATINS

<130> FG0217 PCT

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Glu Asp Ile Pro Pro Val Thr Cys Val Gln Asn Gly Leu Arg Tyr His
              35                  40                  45
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Asp Arg Asp Val Trp Lys Pro Val Pro Cys Gln Ile Cys Val Cys Asp
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Asn Gly Asn Val Leu Cys Asp Asp Val Ile Cys Asp Glu Leu Lys Asp
65              70              75              80

Cys Pro Asn Ala Lys Val Pro Thr Asp Glu Cys Cys Pro Val Cys Pro
                85              90              95

Glu Gly Gln Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly
            100             105             110

Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro
        115             120             125

Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro
    130             135             140

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala
145             150             155             160

Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Thr Gly Ile Ser Val
            165             170             175

Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Pro Gly Pro Pro
        180             185             190

Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro Gly
        195             200             205

Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly Pro
    210             215             220

Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg Pro
225             230             235             240

Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro Gly
            245             250             255

Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly Leu
            260             265             270

Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu Pro
        275             280             285

Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg Gly
    290             295             300

Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly Ala
305             310             315             320

Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro Thr
            325             330             335

Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys Gly
        340             345             350

Glu Gly Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly Val
    355             360             365

3

Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala Gly Pro Ala
    370             375             380

Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn Gly
385             390             395             400

Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly Pro
            405             410             415

Ser Gly Pro Gln Gly Pro Ser Gly Pro Pro Gly Pro Lys Gly Asn Ser
            420             425             430

Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys Gly
        435             440             445

Glu Pro Gly Pro Thr Gly Ile Gln Gly Pro Pro Gly Pro Ala Gly Glu
    450             455             460

Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Ala Gly Leu Pro
465             470             475             480

Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro Gly
            485             490             495

Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly Ala
            500             505             510

Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg Pro
        515             520             525

Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro Gly
    530             535             540

Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly Gln
545             550             555             560

Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln Ala
            565             570             575

Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro Gly
            580             585             590

Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly Pro
        595             600             605

Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro Ala
    610             615             620

Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro Gly
625             630             635             640

Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly Lys
            645             650             655

Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro Ser
        660             665             670

Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln Gly
        675             680             685

4

Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly Asn
    690             695              700

Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser Gln
705             710              715             720

Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala Gly
            725             730             735

Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly Ala
            740             745             750

Asp Gly Ala Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro Ile
        755             760             765

Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ala Gly
    770             775             780

Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly Asp
785             790             795             800

Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro Pro
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Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala Gly
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Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly Pro
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Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Pro Lys Gly Ala Arg
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Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala Gly
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Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly Pro
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Pro Gly Pro Ala Gly Lys Glu Gly Ser Lys Gly Pro Arg Gly Glu Thr
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Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro Gly
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Pro Ala Gly Glu Lys Gly Ala Pro Gly Ala Asp Gly Pro Ala Gly Ala
    930             935             940

Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val Val
945             950             955             960

Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro Gly
            965             970             975

Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly Glu
            980             985             990

Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro Pro
    995             1000            1005

5

Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser Pro Gly
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Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly Pro
1025              1030          1035              1040

Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro Val
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Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala Gly
         1060          1065              1070

Pro Ala Gly Pro Ile Gly Pro Val Gly Ala Arg Gly Pro Ala Gly Pro
    1075          1080              1085

Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp Arg
    1090          1095              1100

Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro Gly
1105              1110          1115              1120

Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly Pro
         1125              1130          1135

Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ser Pro Gly Lys Asp
         1140          1145          1150

Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly
         1155          1160          1165

Arg Thr Gly Asp Ala Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Pro
    1170          1175          1180

Pro Gly Pro Pro Gly Pro Pro Ser Gly Gly Tyr Asp Leu Ser Phe Leu
1185              1190          1195              1200

Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr Arg
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Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp Thr
         1220          1225              1230

Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro Glu
    1235              1240              1245

Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met Cys
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His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln Gly
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Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly Glu
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Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp Tyr
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Ile Ser Lys Asn Pro Lys Glu Lys Arg His Val Trp Tyr Gly Glu Ser
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6

Met Thr Gly Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp Pro
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Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr Glu
1345                1350                1355                1360

Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr Met
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Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Gln Gly Ser
            1380                1385                1390

Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr Ser
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Val Thr Tyr Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys Thr
   1410                1415                1420

Val Ile Glu Tyr Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile Ile Asp
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Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe Asp
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Val Gly Pro Ala Cys Phe Leu
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7

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8

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Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu
        35                  40                  45

Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
    50                  55                  60

Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
65                  70                  75                  80

Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
                85                  90                  95

Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
            100                 105                 110

Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Pro Pro Gly Ser
        115                 120                 125

Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
    130                 135                 140

Pro Thr Gly Gly Gln Asn Tyr Ser Pro Gln Tyr Glu Ala Tyr Asp Val
145                 150                 155                 160

Lys Ser Gly Val Ala Gly Gly Gly Ile Ala Gly Tyr Pro Gly Pro Ala
            165                 170                 175

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
        180                 185                 190

Ala Pro Gly Ala Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
        195                 200                 205

Ala Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
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Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225                 230                 235                 240

Glu Arg Gly Phe Pro Gly Pro Pro Gly Met Lys Gly Pro Ala Gly Met
            245                 250                 255

Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
        260                 265                 270

Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
        275                 280                 285

Val Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
    290                 295                 300

Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
305                 310                 315                 320

Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
            325                 330                 335

Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
        340             345             350

Val Gly Pro Ala Gly Ser Pro Gly Ser Ser Gly Ala Pro Gly Gln Arg
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Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Pro Gly Pro Pro Gly
    370             375             380

Pro Pro Gly Ser Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
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Ala Gly Ile Pro Gly Ala Pro Gly Leu Ile Gly Ala Arg Gly Pro Pro
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Gly Pro Pro Gly Thr Asn Gly Val Pro Gly Gln Arg Gly Ala Ala Gly
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Glu Pro Gly Lys Asn Gly Ala Lys Gly Asp Pro Gly Pro Arg Gly Glu
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Arg Gly Glu Ala Gly Ser Pro Gly Ile Ala Gly Pro Lys Gly Glu Asp
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Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465             470             475             480

Ala Ala Gly Glu Arg Gly Val Pro Gly Phe Arg Gly Pro Ala Gly Ala
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Asn Gly Leu Pro Gly Glu Lys Gly Pro Pro Gly Asp Arg Gly Gly Pro
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Gly Pro Ala Gly Pro Arg Gly Val Ala Gly Glu Pro Gly Arg Asp Gly
        515             520             525

Leu Pro Gly Gly Pro Gly Leu Arg Gly Ile Pro Gly Ser Pro Gly Gly
    530             535             540

Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Thr
545             550             555             560

Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly Gln Pro Gly
            565             570             575

Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
            580             585             590

Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Ala
        595             600             605

Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
        610             615             620

Pro Ser Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
625             630             635             640

Gln Gly Leu Pro Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys Pro
            645             650             655

10

Gly Glu Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro Gly
       660              665             670

Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Ala
    675            680          685

Gly Gly Pro Pro Gly Pro Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
  690           695          700

Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Gly Ser Ala Gly
705          710          715         720

Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Pro Gly Gly
      725          730          735

Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Ser Ser Gly Val Asp
    740          745          750

Gly Ala Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
    755        760         765

Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Ser Gly Ala
  770          775         780

Pro Gly Val Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro Gly Glu Arg
785          790        795         800

Gly Glu Gln Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
      805          810         815

Gln Asn Gly Glu Pro Gly Ala Lys Gly Glu Arg Gly Ala Pro Gly Glu
      820         825         830

Lys Gly Glu Gly Gly Pro Pro Gly Ala Ala Gly Pro Ala Gly Gly Ser
    835        840         845

Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
  850          855         860

Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly Pro
865          870        875        880

Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser Ser
      885         890        895

Gly Ala Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly Ser Asn Gly
      900        905        910

Ala Pro Gly Ser Pro Gly Ile Ser Gly Pro Lys Gly Asp Ser Gly Pro
    915        920        925

Pro Gly Glu Arg Gly Ala Pro Gly Pro Gln Gly Pro Pro Gly Ala Pro
  930          935        940

Gly Pro Leu Gly Ile Ala Gly Leu Thr Gly Ala Arg Gly Leu Ala Gly
945          950        955        960

Pro Pro Gly Met Pro Gly Ala Arg Gly Ser Pro Gly Pro Gln Gly Ile
      965         970        975

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Lys Gly Glu Asn Gly Lys Pro Gly Pro Ser Gly Gln Asn Gly Glu Arg
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Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
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Asp Gly Ala Pro Gly Ala Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro
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Ser Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly Pro Pro Gly Pro Gln
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Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Met Gly
    1090                1095                1100

Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser
1105                1110                1115                1120

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Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly
    1140                1145                1150

Ala Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn
    1155                1160                1165

Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro
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Gly Val Ala Ala Ile Ala Gly Val Gly Ala Glu Lys Ala Gly Gly Phe
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Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
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Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
    1250                1255                1260

Leu Lys Phe Cys His Pro Glu Leu Gln Ser Gly Glu Tyr Trp Val Asp
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Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Tyr Cys Asn Met
         1285                1290                1295
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12

Glu Thr Gly Glu Thr Cys Ile Ser Ala Ser Pro Leu Thr Ile Pro Gln
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Lys Asn Trp Trp Thr Asp Ser Gly Ala Glu Lys Lys His Val Trp Phe
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Gly Glu Ser Met Glu Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
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Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
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Ala Tyr Met Asp His Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu
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Gly Lys Thr Val Phe Gln Tyr Gln Thr Arg Lys Ala Val Arg Leu Pro
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            20               25               30

Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu
        35               40               45

Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
    50               55               60

Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
65               70               75               80

Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
 .           85               90               95

Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
            100              105              110

Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Pro Pro Gly Ser
        115              120      .       125

Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
    130              135              140

Pro Thr Gly Gly Gln Asn Tyr Ser Pro Gln Tyr Glu Ala Tyr Asp Val
145              150      \          155              160

Lys Ser Gly Val Ala Gly Gly Gly Ile Ala Gly Tyr Pro Gly Pro Ala
            165              170              175

Gly Pro Pro Gly Pro Pro Gly Pro Gly Thr Ser Gly His Pro Gly
        180              185              190

Ala Pro Gly Ala Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
        195              200              205

Ala Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
210              215              220

Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225              230              235              240

Glu Arg Gly Phe Pro Gly Pro Pro Gly Met Lys Gly Pro Ala Gly Met
            245              250              255

Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
            260              265              270

Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
            275              280              285

Val Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
            290              295              300
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15

Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
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Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
            325             330             335

Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
            340             345             350

Val Gly Pro Ala Gly Ser Pro Gly Ser Ser Gly Ala Pro Gly Gln Arg
            355             360             365

Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Pro Gly Pro Pro Gly
    370             375             380

Pro Pro Gly Ser Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
385             390             395                 400

Ala Gly Ile Pro Gly Ala Pro Gly Leu Ile Gly Ala Arg Gly Pro Pro
            405             410             415

Gly Pro Pro Gly Thr Asn Gly Val Pro Gly Gln Arg Gly Ala Ala Gly
            420             425             430

Glu Pro Gly Lys Asn Gly Ala Lys Gly Asp Pro Gly Pro Arg Gly Glu
    435             440             445

Arg Gly Glu Ala Gly Ser Pro Gly Ile Ala Gly Pro Lys Gly Glu Asp
    450             455             460

Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465             470             475                 480

Ala Ala Gly Glu Arg Gly Val Pro Gly Phe Arg Gly Pro Ala Gly Ala
            485             490             495

Asn Gly Leu Pro Gly Glu Lys Gly Pro Pro Gly Asp Arg Gly Gly Pro
            500             505             510

Gly Pro Ala Gly Pro Arg Gly Val Ala Gly Glu Pro Gly Arg Asp Gly
            515             520             525

Leu Pro Gly Gly Pro Gly Leu Arg Gly Ile Pro Gly Ser Pro Gly Gly
    530             535             540

Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Thr
545             550             555                 560

Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly Gln Pro Gly
            565             570             575

Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
            580             585             590

Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Ala
    595             600             605

Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
    610             615             620

16

Pro Ser Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
625                 630                 635                 640

Gln Gly Leu Pro Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys Pro
                645                 650                 655

Gly Glu Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro Gly
            660                 665                 670

Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Ala
            675                 680                 685

Gly Gly Pro Pro Gly Pro Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
    690                 695                 700

Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ser Ala Gly
705                 710                 715                 720

Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Pro Gly Gly
                725                 730                 735

Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Ser Ser Gly Val Asp
            740                 745                 750

Gly Ala Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
            755                 760                 765

Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Ser Gly Ala
    770                 775                 780

Pro Gly Val Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro Gly Glu Arg
785                 790                 795                 800

Gly Glu Gln Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
                805                 810                 815

Gln Asn Gly Glu Pro Gly Ala Lys Gly Glu Arg Gly Ala Pro Gly Glu
            820                 825                 830

Lys Gly Glu Gly Gly Pro Pro Gly Ala Ala Gly Pro Ala Gly Gly Ser
            835                 840                 845

Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
    850                 855                 860

Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly Pro
865                 870                 875                 880

Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser Ser
                885                 890                 895

Gly Ala Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly Ser Asn Gly
            900                 905                 910

Ala Pro Gly Ser Pro Gly Ile Ser Gly Pro Lys Gly Asp Ser Gly Pro
            915                 920                 925

Pro Gly Glu Arg Gly Ala Pro Gly Pro Gln Gly Pro Pro Gly Ala Pro
    930                 935                 940

17

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Gly Pro Leu Gly Ile Ala Gly Leu Thr Gly Ala Arg Gly Leu Ala Gly
945             950             955             960

Pro Pro Gly Met Pro Gly Ala Arg Gly Ser Pro Gly Pro Gln Gly Ile
            965             970             975

Lys Gly Glu Asn Gly Lys Pro Gly Pro Ser Gly Gln Asn Gly Glu Arg
        980             985             990

Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
        995             1000            1005

Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg
    1010            1015            1020

Asp Gly Ala Pro Gly Ala Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro
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Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly
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Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala Gly Pro
        1060            1065            1070

Ser Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly Pro Pro Gly Pro Gln
    1075            1080            1085

Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Met Gly
    1090            1095            1100

Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser
1105            1110            1115            1120

Pro Gly Pro Ala Gly His Gln Gly Ala Val Gly Ser Pro Gly Pro Ala
            1125            1130            1135

Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly
        1140            1145            1150

Ala Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn
        1155            1160            1165

Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro
    1170            1175            1180

Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Ala Gly
1185            1190            1195            1200

Gly Val Ala Ala Ile Ala Gly Val Gly Ala Glu Lys Ala Gly Gly Phe
            1205            1210            1215

Ala Pro Tyr Tyr Gly Asp Glu Pro Ile Asp Phe Lys Ile Asn Thr Asn
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Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
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Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
    1250            1255            1260
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18

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L u Lys Phe Cys His Pro Glu Leu Gln Ser Gly Glu Tyr Trp Val Asp
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Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Tyr Cys Asn Met
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Glu Thr Gly Glu Thr Cys Ile Ser Ala Ser Pro Leu Thr Ile Pro Gln
          1300              1305             1310

Lys Asn Trp Trp Thr Asp Ser Gly Ala Glu Lys Lys His Val Trp Phe
          1315              1320             1325

Gly Glu Ser Met Glu Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
       1330              1335             1340

Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
1345              1350             1355             1360

Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile
          1365              1370             1375

Ala Tyr Met Asp His Val Ser Gly Asn Val Lys Lys Ala Leu Lys Leu
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Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe
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Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp
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Gly Lys Thr Val Phe Gln Tyr Gln Thr Arg Lys Ala Val Arg Leu Pro
1425              1430             1435             1440

Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
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Gly Gln Glu Glu Asp Ile Pro Pro Val Thr Cys Val Gln Asn Gly Leu
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Arg Tyr His Asp Arg Asp Val Trp Lys Pro Val Pro Cys Gln Ile Cys
    50                  55                  60

Val Cys Asp Asn Gly Asn Val Leu Cys Asp Asp Val Ile Cys Asp Glu
65                  70                  75                  80

Ile Lys Asn Cys Pro Ser Ala Arg Val Pro Ala Gly Glu Cys Cys Pro
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Val Cys Pro Glu Gly Glu Val Ser Pro Thr Asp Gln Glu Thr Thr Gly
            100                 105                 110

Val Glu Gly Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro
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Ser Gly Pro Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro
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Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly
145                 150                 155                 160

Asn Phe Ala Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Ala Gly
                165                 170                 175

Ile Ser Val Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Ser
            180                 185                 190

Gly Pro Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly
        195                 200                 205

Glu Pro Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro
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Pro Gly Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro
225                 230                 235                 240

Gly Arg Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly
                245                 250                 255

Leu Pro Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe
            260                 265                 270

21

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Ser Gly Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys
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Gly Glu Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly
    290             295             300

Pro Arg Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Pro Pro Gly Pro
305             310             315             320

Ala Gly Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro
            325             330             335

Gly Pro Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly
            340             345             350

Ala Lys Gly Glu Ala Gly Pro Gln Gly Ala Arg Gly Ser Glu Gly Pro
    355             360             365

Gln Gly Val Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala
    370             375             380

Gly Pro Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Gly Lys Gly
385             390             395             400

Ala Asn Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala
            405             410             415

Arg Gly Pro Ser Gly Pro Gln Gly Pro Ser Gly Pro Pro Gly Pro Lys
            420             425             430

Gly Asn Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly
            435             440             445

Ala Lys Gly Glu Pro Gly Pro Thr Gly Val Gln Gly Pro Pro Gly Pro
    450             455             460

Ala Gly Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Ala
465             470             475             480

Gly Leu Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly
            485             490             495

Phe Pro Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu
            500             505             510

Arg Gly Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala
            515             520             525

Gly Arg Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly
    530             535             540

Ser Pro Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro
545             550             555             560

Ala Gly Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg
            565             570             575

Gly Gln Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly
            580             585             590
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Glu Pro Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala
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Val Gly Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro
    610             615             620

Gly Pro Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly
625             630             635             640

Ser Pro Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu
            645             650             655

Ala Gly Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro
        660             665             670

Gly Pro Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly
        675             680             685

Val Gln Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala
    690             695             700

Pro Gly Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro
705             710             715             720

Gly Ser Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly
            725             730             735

Ala Ala Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro
        740             745             750

Lys Gly Ala Asp Gly Ala Pro Gly Lys Asp Gly Val Arg Gly Leu Thr
        755             760             765

Gly Pro Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly
    770             775             780

Glu Thr Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala
785             790             795             800

Pro Gly Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala
            805             810             815

Gly Pro Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Gly Pro Thr
        820             825             830

Gly Pro Pro Gly Pro Ile Gly Ser Val Gly Ala Pro Gly Pro Lys Gly
        835             840             845

Ala Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala
    850             855             860

Ala Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro
865             870             875             880

Gly Pro Pro Gly Pro Ala Gly Lys Glu Gly Ser Lys Gly Pro Arg Gly
            885             890             895

Glu Thr Gly Pro Ala Gly Arg Pro Gly Glu Ala Gly Pro Pro Gly Pro
        900             905             910

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Pro Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala
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Gly Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly
  930              935            940

Val Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu
945           950           955           960

Pro Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Pro Ser
         965             970             975

Gly Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly
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Pro Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser
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Pro Gly Arg Asp Gly Ala Pro Gly Pro Lys Gly Asp Arg Gly Glu Ser
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Gly Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly
1025         1030          1035        1040

Pro Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro
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Ala Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala
        1060         1065         1070

Gly Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly
     1075         1080          1085

Asp Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro
  1090          1095         1100

Pro Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser
1105         1110          1115        1120

Gly Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly
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Lys Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro
        1140         1145         1150

Arg Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro
     1155         1160         1165

Gly Pro Pro Gly Pro Pro Gly Pro Ser Gly Gly Phe Asp Phe Ser
  1170          1175         1180

Phe Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr
1185         1190          1195        1200

Tyr Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val
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Asp Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser
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Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys
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Met Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn
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Gln Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr
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Gly Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Pro Gln Lys Asn
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Trp Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Tyr Gly
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Glu Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Glu Gly Ser
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Asp Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser
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Thr Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala
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Tyr Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Gln
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Gly Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr
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Tyr Ser Val Ile Tyr Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly
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Lys Thr Val Ile Glu Tyr Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile
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Ile Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly
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Ile Asp Leu Ser Pro Val Cys Phe Leu
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Gly Pro Thr Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly
         35                  40                  45

Pro Pro Gly Arg Asp Gly Asp Asp Gly Ile Pro Gly Pro Pro Gly Pro
     50                  55                  60

Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln
 65                  70                  75                  80

Tyr Asp Gly Lys Gly Val Gly Ala Gly Pro Gly Pro Met Gly Leu Met
             85                  90                  95

Gly Pro Arg Gly Pro Pro Gly Ala Val Gly Ala Pro Gly Pro Gln Gly
             100                 105                 110

Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro
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Ala Gly Ala Arg Gly Pro Pro Gly Pro Pro Gly Lys Ala Gly Glu Asp
     130                 135                 140

Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
145                 150                 155                 160

Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
                 165                 170                 175

Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
             180                 185                 190

Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
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Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
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Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Asn Asp Gly Ser Val
225                 230                 235                 240
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27

Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly
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Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Leu Gly Pro Val Gly Asn
              260                     265                 270

Pro Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
              275                     280                 285

Gly Val Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
    290                     295                 300

Leu Pro Gly Ala Lys Gly Ala Ala Gly Leu Leu Gly Val Ala Gly Ala
305                     310                 315                 320

Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Ala Gly Ala Ala
              325                     330                 335

Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
              340                     345                 350

Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ala Ala Gly Pro
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Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
    370                     375                 380

Gly Glu Val Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
385                     390                 395                 400

Asn Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
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Met Gly Pro Pro Gly Ser Arg Gly Pro Thr Gly Pro Ala Gly Val Arg
              420                     425                 430

Gly Pro Asn Gly Asp Ser Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
              435                     440                 445

Pro Arg Gly Phe Pro Gly Ser Pro Gly Asn Val Gly Pro Ala Gly Lys
    450                     455                 460

Glu Gly Pro Ala Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
465                     470                     475             480

Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
              485                     490                 495

Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Glu Lys Gly His
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Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
              515                     520                 525

Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
    530                     535                 540

Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
545                     550                     555             560

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Ala Gly Thr Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Ile Pro
              565                 570                 575

Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
              580                 585                 590

Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Ala Gly Pro Ile Gly Ser
          595                 600                 605

Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
    610                 615                 620

Gly Val Leu Gly Ala Pro Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly
625                 630                 635                 640

Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu
              645                 650                 655

Lys Gly Glu Thr Gly Leu Arg Gly Asp Val Gly Ser Pro Gly Arg Asp
              660                 665                 670

Gly Ala Arg Gly Ala Pro Gly Ala Val Gly Ala Pro Gly Pro Ala Gly
          675                 680                 685

Ala Asn Gly Asp Arg Gly Glu Ala Gly Pro Ala Gly Pro Ala Gly Pro
    690                 695                 700

Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala
705                 710                 715                 720

Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly
              725                 730                 735

Ala Lys Gly Glu Arg Gly Thr Lys Gly Pro Lys Gly Glu Asn Gly Pro
              740                 745                 750

Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn
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Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly
    770                 775                 780

Ala Thr Gly Phe Pro Gly Ala Ala Gly Arg Ile Gly Pro Pro Gly Pro
785                 790                 795                 800

Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu
              805                 810                 815

Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
          820                 825                 830

Glu Thr Gly Ala Ser Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
          835                 840                 845

Ser Gly Glu Pro Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln
    850                 855                 860

Gly Ile Leu Gly Ala Pro Gly Phe Leu Gly Leu Pro Gly Ser Arg Gly
865                 870                 875                 880

29

Glu Arg Gly Leu Pro Gly Val Ala Gly Ser Val Gly Glu Pro Gly Pro
          885              890              895

Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val
          900              905      .       910

Gly Asn Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly
          915              920              925  .         .

Asn Pro Gly Ser Asp Gly Pro Pro Gly Arg Asp Gly Gln Ala Gly His
    930              935  .           940

Lys Gly Glu Arg Gly Tyr Pro Gly Asn Pro Gly Pro Ala Gly Ala Ala
945              950              955              960

Gly Ala Pro Gly Pro Gln Gly Ala Val Gly Pro Ala Gly Lys His Gly
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Asn Arg Gly Glu Pro Gly Pro Ala Gly Ser Val Gly Pro Ala Gly Ala
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Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Glu Lys
          995              1000             1005

Gly Glu Pro Gly Asp Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly
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His Asn Gly Leu Gln Gly Leu Pro Gly Leu Ala Gly His His Gly Asp
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Gln Gly Ala Pro Gly Pro Val Gly Pro Ala Gly Pro Arg Gly Pro Ala
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Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly Gln Pro Gly
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Ala Val Gly Pro Ala Gly Ile Arg Gly Ser Gln Gly Ser Gln Gly Pro
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Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Ser
    1090             1095             1100

Gly Gly Gly Tyr Asp Phe Gly Tyr Glu Gly Asp Phe Tyr Arg Ala Asp
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Gln Pro Arg Ser Pro Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp
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Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro
          1140  .           1145             1150

Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu
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Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln
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Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly
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Tyr Arg Asn Ser Lys Val Lys Lys His Val Trp Leu Gly Glu Thr Ile
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Asn Gly Gly Thr Gln Phe Glu Tyr Asn Met Glu Gly Val Thr Thr Lys
        1235                1240                1245

Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn His Ala
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Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp
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Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn
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Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val
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Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Arg Lys Thr Ile
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Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Ile Leu Asp Ile
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Cys Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro
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Glu Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp
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Asp Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile
65　　　　　　　　　　70　　　　　　　　　75　　　　　　　　　　80

Pro Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro
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Thr Arg Pro Pro Asn Gly His Gly Pro Gln Gly Pro Lys Gly Asp Pro
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Gly Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Leu Pro Gly
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Gln Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser
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Cys Pro Thr Gly Gly Gln Asn Tyr Ser Pro Gln Tyr Glu Ser Tyr Asp
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Val Lys Ala Gly Val Ala Gly Gly Gly Ile Gly Gly Tyr Pro Gly Pro
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Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser Gly His Pro
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Gly Ala Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly
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Gln Ala Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro
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Ser Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro
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Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Leu Lys Gly Pro Ala Gly
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Met Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg
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Asn Gly Glu Lys Gly Asp Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn
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Gly Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly
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Ala Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala
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Gly Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly
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Pro Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro
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Gly Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly
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Glu Arg Gly Glu Ala Gly Ser Pro Gly Ile Pro Gly Pro Lys Gly Glu
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Asp Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro
465                470                475                480

Gly Ala Ala Gly Glu Arg Gly Met Pro Gly Phe Arg Gly Ala Pro Gly
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Ala Asn Gly Leu Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Gly
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Pro Gly Pro Ala Gly Pro Arg Gly Val Ala Gly Glu Pro Gly Arg Asp
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Gly Val Pro Gly Gly Pro Gly Leu Arg Gly Met Pro Gly Ser Pro Gly
   530                535                540

Gly Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu
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Ser Gly Arg Pro Gly Pro Pro Gly Ser Pro Gly Pro Arg Gly Gln Pro
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Gly Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly
          580                585                590

Lys Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Leu Pro Gly Pro
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Pro Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr
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34

Gly Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Gln Gln Gly
625                 630                 635                 640

Leu Gln Gly Leu Pro Gly Thr Ser Gly Pro Pro Gly Glu Asn Gly Lys
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Pro Gly Glu Pro Gly Pro Lys Gly Glu Ala Gly Ala Pro Gly Ile Pro
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Gly Gly Lys Gly Asp Ser Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly
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Ala Val Gly Pro Ser Gly Pro Arg Gly Gly Ala Gly Pro Pro Gly Pro
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Gly Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Ser Gly
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Gly Pro Gly Pro Lys Gly Asp Lys Gly Asp Pro Gly Gly Ser Gly Ala
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Asp Gly Ala Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile
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Ala Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Gly Pro Gly Glu
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Arg Gly Glu His Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro
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Gly Gln Asn Gly Glu Pro Gly Ala Lys Gly Glu Arg Gly Ala Pro Gly
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Glu Lys Gly Glu Gly Gly Pro Pro Gly Ile Ala Gly Gln Pro Gly Gly
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Thr Gly Pro Pro Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg
850                 855                 860

Gly Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Gly Arg Gly
865                 870                 875                 880

Leu Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Ser
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Ser Gly Pro Pro Gly Lys Asp Gly Pro Pro Gly Pro Pro Gly Ser Ser
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Gly Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly
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Gln Pro Gly Glu Lys Gly Ser Pro Gly Pro Gln Gly Pro Pro Gly Ala
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35

Pro Gly Pro Gly Gly Ile Ser Gly Ile Thr Gly Ala Arg Gly Leu Ala
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Gly Pro Pro Gly Met Pro Gly Ala Arg Gly Ser Pro Gly Pro Gln Gly
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Val Lys Gly Glu Asn Gly Lys Pro Gly Pro Ser Gly Leu Asn Gly Glu
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Arg Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Ala Ala
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Gly Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly
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Arg Asp Gly Ala Pro Gly Ser Lys Gly Asp Arg Gly Glu Asn Gly Ser
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Pro Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val
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Gly Pro Ala Gly Lys Asn Gly Asp Arg Gly Glu Thr Gly Pro Ala Gly
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Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Asn
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Gly Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly
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Ser Pro Gly Pro Ala Gly His Gln Gly Ala Val Gly Ser Pro Gly Pro
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Ala Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp
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Asn Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln
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Pro Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly
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Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
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Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
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Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
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36

Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp
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Glu Thr Gly Glu Thr Cys Ile Ser Ala Ser Pro Ser Thr Val Pro Arg
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Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
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Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile
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Ala Tyr Met Glu His Ala Ser Gly Asn Val Lys Lys Ala Leu Arg Leu
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